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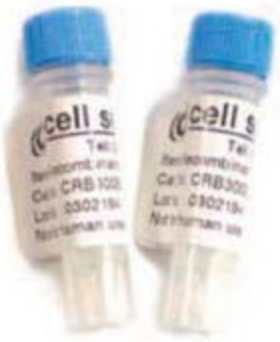

PROTEINS

4-1BBL
4-1BB Receptor
6 Ckine
ACAD8
ACAT2
gAcrp30/Adipolean
Activin A
Activin B
ACY1
ADAT1
Adiponectin
ADRP
AITRL
Akt1
Alpha-Feto Protein (AFP)
Alpha-Galactosidase A
Angiopoietin-1 (Ang-1)
Angiopoietin-2 (Ang-2)
Angiostatin K1-3
Annexin-V
apo-SAA
Apoliprotein A-1
Apoliprotein E2
Apoliprotein E3
Apoliprotein E4
APRIL
Artemin
ATF2
Aurora A
Aurora B
BAFF
BAFF Receptor
BCA-1 / BLC / CXCL13
BCMA
BD-1
BD-2
BD-3
BDNF
Betacellulin
Bivalirudin
BMP-2
BMP-4
BMP-6
BMP-7
BMP-13
sBMPR-1A
Brain Natriuretic Protein
BRAK
Breast Tumor Antigen
C5a
C5L2 Peptide
C-10
C-Reactive Protein
C-Src
Calbindin D-9K
Calbindin D-28K
Calbindin D-29K
Calmodulin
Calcitonin Acetate
Carbonic Anhydrase III
Carcino-embryonic Antigen
Cardiotrophin-1
Caspase-3
Caspase-6
CD4
CD14
CD22
CD40 Ligand / TRAP
CD95 / sFas Ligand
CD105 / Endoglin
CHIPS
CNTF
Collagen
CREB
CTACK / CCL27
CTGF
CTGFL / WISP-2
CTLA-4 / Fc
CXCL16
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Cytokeratin 8
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Desmopressin
Disulfide Oxidoreductase
E-selectin
ECGF
EGF
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ENA-78 / CXCL5
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EPHB2
EPHB4
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Epiregulin
Eptifbatide
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Exodus-2
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Fas Receptor
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FGF-2 (basic)
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sFGFR-2 (IIIc) / Fc Chimera
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sFGFR-4 / Fc Chimera
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sFlt-1 (D3)
sFlt-1 (D4)
sFlt-1 (D5)
sFlt-1 (D7)
Flt3-Ligand
sFlt-4
sFlt-4 / Fc Chimera
Follistatin
FSH
Fractalkine / CX3C
G-CSF
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Galectin-1
Galectin-3
Gastrointestinal CA
GCP-2
GDF-3
GDF-9
GDF-11
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GPBB
Granzyme B
GROα
GROβ
GROγ
GRO/MGSA
Growth Hormone
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GST-p21/WAF-1
HB-EGF
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HGF
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Histrelin
HRG1-β1
I-309
I-TAC
IFN-α
IFN-α A
IFN-α 2a
IFN-α 2b
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IFN-Omega
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IGF-II
proIGF-II
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Oncostatin M
Osteoprotegerin (OPG)
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p38-α
PAI-1
Parathyroid Hormone
PDGF-AA
PDGF-AB
PDGF-BB
PDGF-CC
Persephin
PF-4
PIGF-1
PIGF-2
PKA α-subunit
PKC-α
PKC-γ
Pleiotrophin
PLGF-1
Polymyxin B (PMB)
PRAS40
PRL-1
PRL-2
PRL-3
Prokineticin-2
Prolactin
Protirelin
PTHrP
PTP1B
PTP-IA2
PTP-MEG2
PTP-PEST
sRANK
sRANKL
RANTES
RELM-α
RELM-β
Resistin
RPTPβ
RPTPγ
RPTPμ
SCF
SCGF-α
SCGF-β
SDF-1α
SDF-1β
Secretin
SF20
SHP-2
STAT1
c-Src
TACI
TARC
TC-PTP
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TFF2
TGF-α
TGF-β1
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TGF-β3
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sTIE-1/Fc Chimera
sTIE-2/Fc Chimera
TL-1A
TNF-α
TNF-β
sTNF-receptor Type I
sTNF-receptor Type II
TPO
sTRAIL R-1 (DR4)
sTRAIL R-2 (DR5)
TRAIL/Apo2L
TSG
TSH
TSLP
TWEAK
TWEAK Receptor
Urokinase
EG-VEGF
VEGF121
VEGF145
VEGF165
VEGF-C
VEGF-C I125
VEGF-E
HB-VEGF-E
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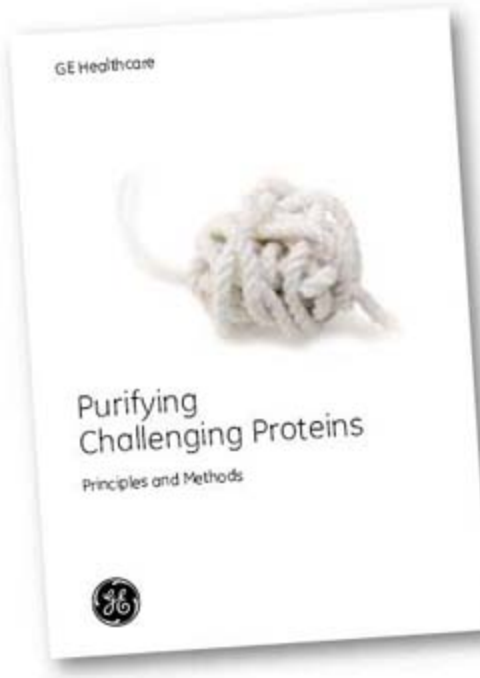

imagination at work

GE19 -07. First printed 07/2007.

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Red tide. The molecular core of a family of red tide toxins can be synthesized by heating a precursor of linked rings (epoxides) in water, which promotes a cascading transformation that produces the characteristic ladder-shaped motif. These results highlight water's dramatic effects on reactivity and selectivity in organic reactions. See page 1189.

Photo: Pete Atkinson/Getty Images

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Richard Kerr
2006 Geological Society of America: Public Service Award

Colin Norman
News Editor, *Science* magazine

Jennifer Couzin
Articles selected for inclusion in The Best American Science Writing 2007 and 2005

2003 Evert Clark/Seth Payne Award for Young Science Journalists

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ATMOSPHERIC SCIENCE

Toward Direct Measurement of Atmospheric Nucleation
M. Kulmala et al.
A ubiquitous pool of neutral, nanometer-sized particle clusters dominates the process of aerosol formation over boreal forests.
10.1126/science.1144124

MOLECULAR BIOLOGY

Demethylation of H3K27 Regulates Polycomb Recruitment and H2A Ubiquitination
M. G. Lee et al.
The histone H3 lysine-27 demethylase in humans has been identified.
10.1126/science.1149042

DEVELOPMENTAL BIOLOGY

Target Protectors Reveal Dampening and Balancing of Nodal Agonist and Antagonist by miR-430
W.-Y. Choi, A. J. Giraldez, A. F. Schier
A novel technology to disrupt miRNA-mRNA interactions reveals that some miRNAs may repress antagonistic developmental regulators.
10.1126/science.1147535

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Widespread Lateral Gene Transfer from Intracellular Bacteria to Multicellular Eukaryotes
J. C. Dunning Hotopp et al.
Gene transfer from the symbiont *Wolbachia* to different species of hosts, including insects and nematodes, is found to encompass a range of genes, some comprising almost the entire genome.
10.1126/science.1142490

TECHNICAL COMMENT ABSTRACT

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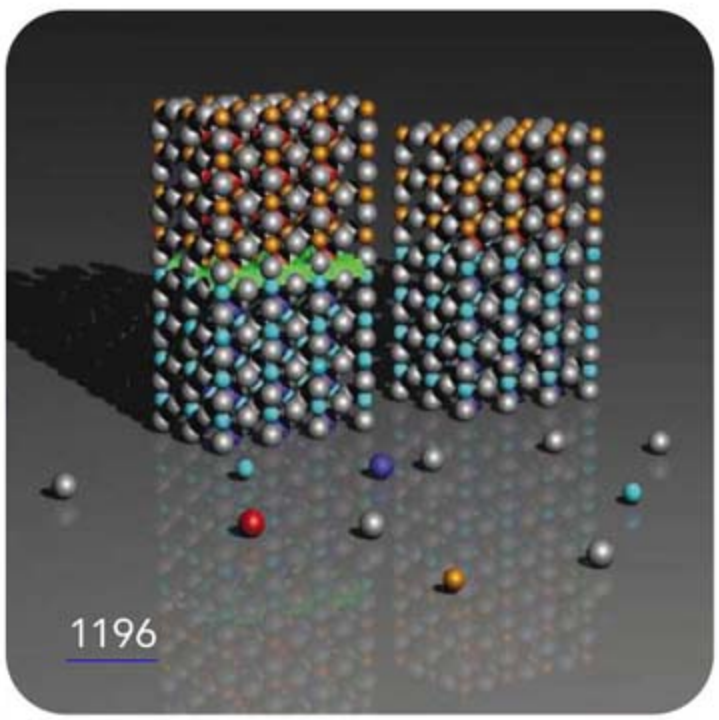

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Coupled Ferric Oxides and Sulfates on the Martian Surface 1206

J.-P. Bibring et al.

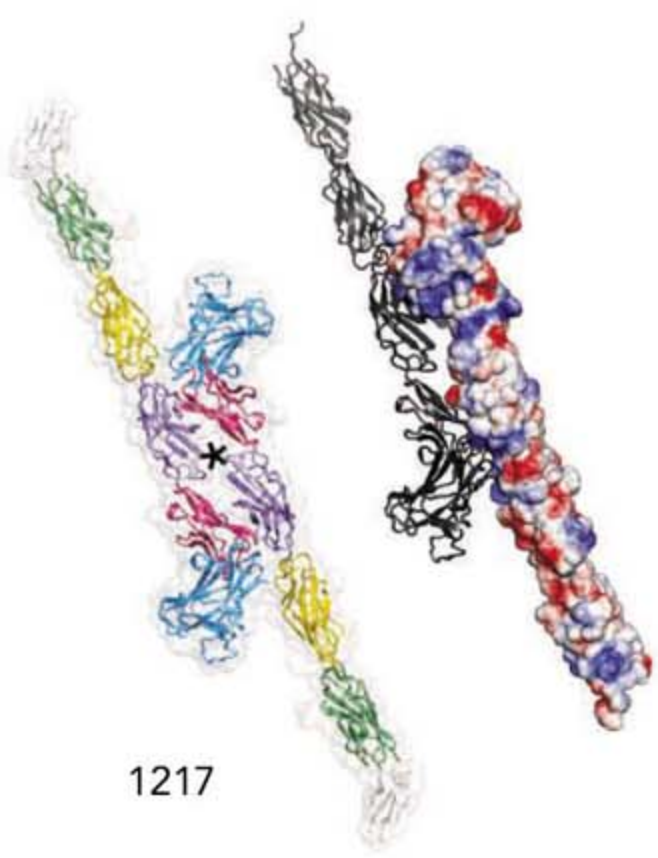
Satellite observations show that oxidized iron minerals appear with sulfate deposits in ancient rocks on Mars, suggesting that acidic groundwater pervaded several regions.

MOLECULAR BIOLOGY

Strand-Biased Spreading of Mutations During Somatic Hypermutation 1227

S. Unniraman and D. G. Schatz

The mutations that underlie antibody diversity are created by error-prone DNA repair triggered in the nontemplate DNA strand but not in the template strand.



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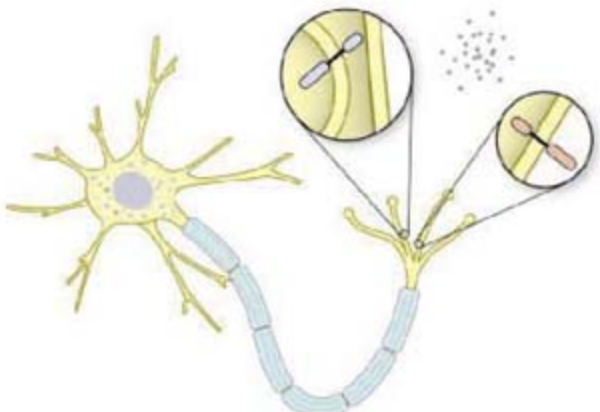
Astronomers find a gigantic zone with no matter in deep space.

Making Sense of Baby Talk
Two studies shed light on how rhesus monkeys and humans speak to infants.



Neuronal Toll-like receptors.

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PERSPECTIVE: Toll-Like Receptors in Brain Development and Homeostasis
P. H. Larsen, T. H. Holm, T. Owens
Toll-like receptors participate in development of the central nervous system and in the response to injury.

PERSPECTIVE: T Cell Activation by TLRs—A Role for TLRs in the Adaptive Immune Response
H. MacLeod and L. M. Wetzler
An agonist of the Toll-like receptor TLR2 activates T_H1 but not T_H2 helper T cells.

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P. Gosling and B. Noordam
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A. vandenBerg
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M. P. DeWhyse
Micella reflects on recent conferencing escapades and confronts the question every first-year postdoc is asking: What now?

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A. Michels
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oxidized pyrimidines	oxidation	✓
deaminated cytosine	hydrolysis	✓
fragmentation	hydrolysis nucleases shearing	X
Protein-DNA crosslinks	formaldehyde	X

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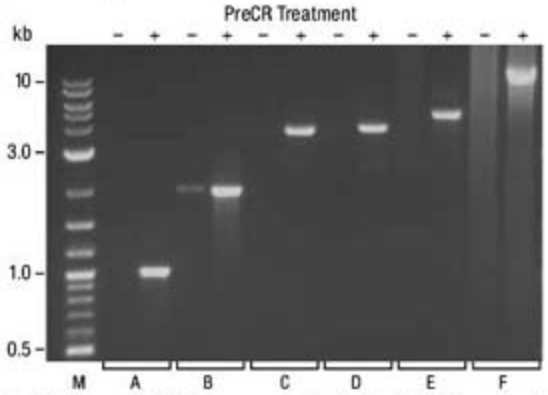

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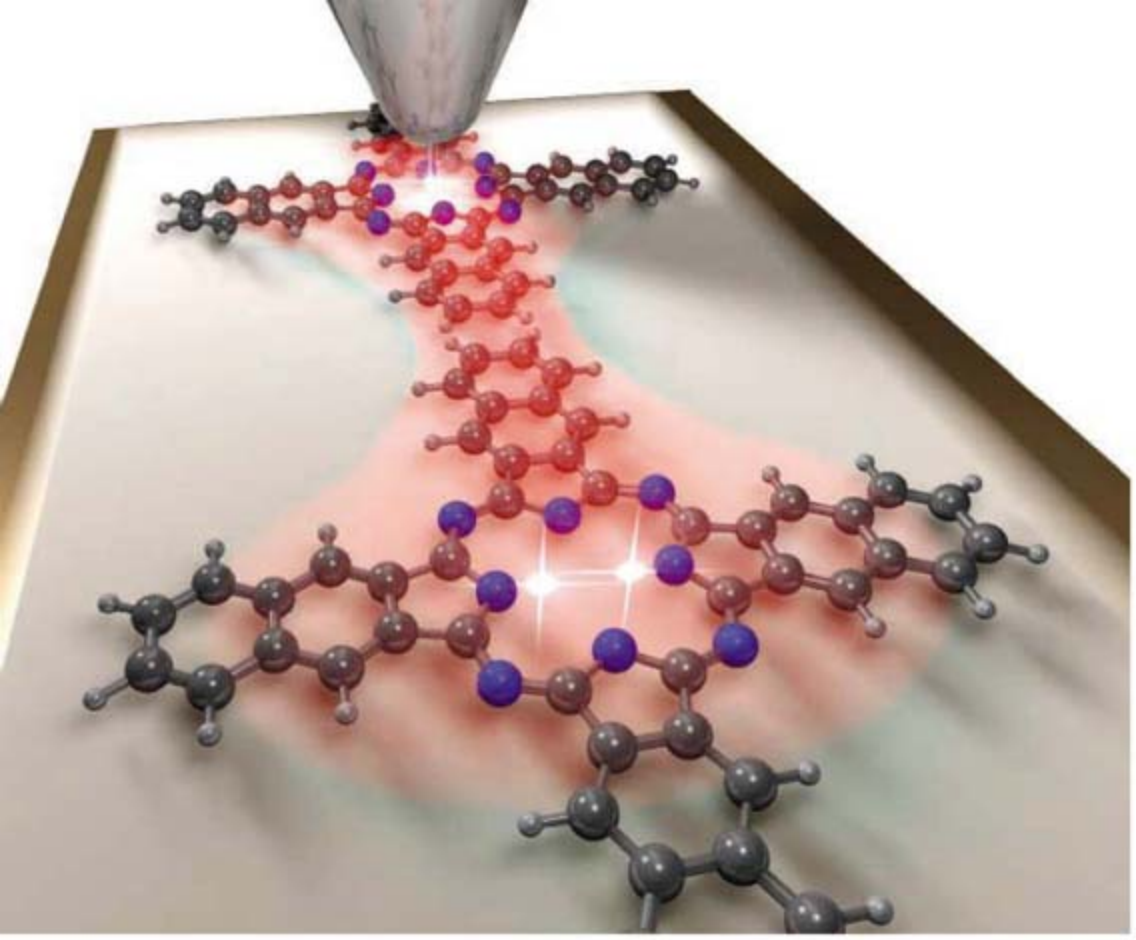


<< Molecular Switching via Hydrogen Hopping

Large changes in conformation can be expected to change the conductivity of a molecule; in device applications, small changes can help maintain geometries favorable for bonding the molecule to its contacts or allowing it to interact with other switching molecules. **Liljeroth *et al.*** (p. 1203) show that the position of the two internal hydrogen atoms on the inner cavity of free-base naphthalocyanine molecules can be switched under cryogenic conditions using the tip of a scanning tunneling microscope (STM). Creation of the new hydrogen tautomer changed the conductance of the molecule. When the molecules were pushed into a chain with the STM tip, a current pulse in an end molecule could induce hydrogen-atom switching in its neighbor.

Aqueous Cascade

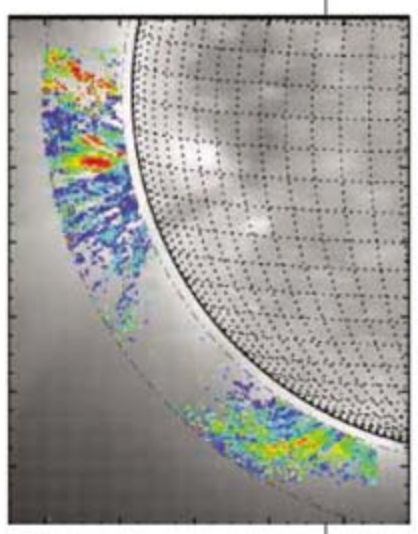
When biosynthetic pathways prove hard to replicate in laboratory model systems, the discrepancy is often attributed to the structural complexity of enzymes. Such was the case for the ladder polyethers, a class of marine toxins associated with red tides. The core of linked tetrahydropyran (THP) cycles appeared most likely to stem from a precursor of multiple epoxides poised for a cascade of consecutive ring-openings, but for more than 20 years, the requisite selectivity for this sequence could not be replicated without adding numerous unnatural substituents needed to direct the reaction. **Vilotijevic and Jamison** (p. 1189; see the news story by **Service**; see the cover) show that the problem was the focus on organic solvent media. Neutral water proved an optimal promoter for the reaction and afforded the polycyclic core in good yield and selectivity from an epoxide chain precursor anchored by a single templating THP.

Sustainable Tropical Forest Management?

The development of conservation strategies in tropical forests requires the assessment of current practices. **Oliveira *et al.*** (p. 1233, published online 9 August 2007) used an automated satellite analysis system to detect both forest disturbances and deforestation, down to the level of a few tree falls, caused by natural and anthropogenic processes in the Peruvian Amazon between 1999 and 2005. Although forest disturbances and deforestation have increased recently, three factors have combined to protect the forests: conservation strategies protect against poaching and clearing; the titling of indigenous territories has protected against deforestation and disturbances; and logging concessions have decreased deforestation in the timber harvest areas. Thus, a portfolio of land-use policies can provide broad protection while still allowing for tribal subsistence and income generation.

Solar Heat Waves

The solar corona is extremely hot gas, extending from the surface of the Sun to millions of kilometers into space. Plasma waves, including incompressible Alfvén waves transmitted along electromagnetic field lines, are thought to be important in heating this gas to temperatures above a million kelvin, but such waves have remained undetected. **Tomczyk *et al.*** (p. 1192) have now imaged the Sun and detected the characteristic pattern of Alfvén waves traveling across its surface with a period of about 5 minutes. However, the waves are weaker in strength than predicted, which suggests that other mechanisms are needed to heat the solar corona.



Martian Ferric Oxides

The geological history of Mars is partly recorded in the various minerals in rocks and soils exposed at its surface. Using infrared spectral data from the Mars Express satellite in orbit around the planet, **Bibring *et al.*** (p. 1206, published online 2 August 2007) show that hematite, formed from oxidized iron, is closely associated with layered sulfate deposits across several of the older terranes on Mars. The oxides formed either contemporaneously or subsequent to the sulfates. Finding this association across different regions implies that rising acidic groundwater conditions were pervasive at the time these minerals were formed.

Magnetic Anisotropy of Embedded Atoms

On a per-atom basis, small molecular magnets and isolated atoms on surfaces can exhibit large anisotropies in their magnetic response with the direction of the applied field at cryogenic temperatures. **Hirjibehedin *et al.*** (p. 1199) have used a scanning tunneling microscope to place iron and manganese atoms in a thin layer of copper nitride and measured their magnetic properties at 0.5 kelvin. The large anisotropies observed are explained by density functional calculations, which indicate that these atoms are covalently incorporated into the CuN layer and transfer charge and spin polarization into the surrounding network.

Continued on page 1143

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Science

AAAS

Continued from page 1141

Superconducting in the Middle

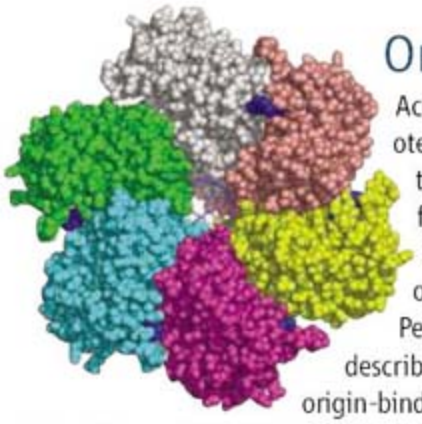
Recent work has revealed that the interface between two oxide insulators, $LaAlO_3$ and $SrTiO_3$, can be metallic. In addition, the conductivity of the interface depends on the thickness of the overlayer. **Reyren *et al.*** (p. 1196, published online 2 August 2007) now show that this interface can also be made superconducting, albeit at low temperatures (200 millikelvin), and show that the properties display signatures of a transition expected for a two-dimensional superconductor.

MicroRNAs and Parkinson's Disease

A variety of nonprotein coding RNA transcripts play roles in development. **Kim *et al.*** (p. 1220; see the Perspective by **Hébert and De Strooper**) now demonstrate a role for microRNAs in the maturation, function, and survival of midbrain dopaminergic neuron cells that are lost in Parkinson's disease. Loss of microRNAs in postmitotic midbrain dopamine neurons leads to a phenotype that resembles Parkinson's disease. The microRNA miR-133b is specifically expressed in human midbrain dopaminergic neurons and is lost in Parkinson's patients. miR-133b functions in a feedback loop with Pitx3, a critical transcriptional regulator of midbrain dopaminergic neurons.

AID Asymmetry

During somatic hypermutation (SHM), antibody genes that have already generated diversity through somatic rearrangement can diversify further. The enzyme responsible for SHM, activation-induced cytidine deaminase (AID), deaminates cytosines to generate uracils in the DNA strand. This reaction initiates subsequent mutations of adjacent residues through the DNA repair process. **Unniraman and Schatz** (p. 1227) now show that SHM is an asymmetric process, with only cytosine residues on the nontemplate strand provoking mutations upstream and downstream. AID targets both strands so it cannot be the source of this asymmetry. Instead, the DNA base-repair system was responsible.



CREDIT: GEORGESCU AND O'DONNELL

Origins and ORCs

Accurate initiation of DNA replication is essential to life. In eukaryotes and archaea, replication initiation is regulated by adenosine triphosphatases of the origin recognition complex (ORC) superfamily that bind to replication origins and prime the DNA for replisomal assembly. Two studies now describe the structural basis for origin recognition by the archaeal initiation factor Orc1 (see the Perspective by **Georgescu and O'Donnell**). **Gaudier *et al.*** (p. 1213) describe the structure of a single Orc1 subunit in complex with its target origin-binding site, and **Dueber *et al.*** (p. 1210) describe the structure of a pair of Orc1 paralogs bound to a second class of origin sequences. Together, the structures provide insight into the stepwise process leading to initiator assembly and activation.

Learning and Recall

During memory encoding, cell assemblies are thought to be activated and linked together by synaptic plasticity. During subsequent retrieval, it is thought that these assemblies may be reactivated by partial activation and pattern completion. **Reijmers *et al.*** (p. 1230) developed mutant mice that allowed active neurons to be tagged differentially during acquisition and retrieval of contextual fear conditioning. In histological sections of the basolateral amygdala the number of neurons that were active during both encoding and retrieval could be counted. Successful memory retrieval was associated with reactivation of neurons that fired during learning.

Intricacies of Cell Contacts

Cell-cell contacts in multicellular organisms are intricately regulated, and their stability is partly controlled by protein kinases and phosphatases that tune the level of tyrosine phosphorylation. Type IIB receptor protein tyrosine phosphatases (RPTPs) have both adhesive and catalytic properties. **Aricescu *et al.*** (p. 1217) determined the crystal structure of the full-length extracellular region of an RPTP, which forms a homophilic trans dimer that is rigid and has dimensions that match the intercellular distance at cadherin-mediated junctions. The trans interaction may act as a spacer clamp that localizes phosphatase activity near its target substrates.

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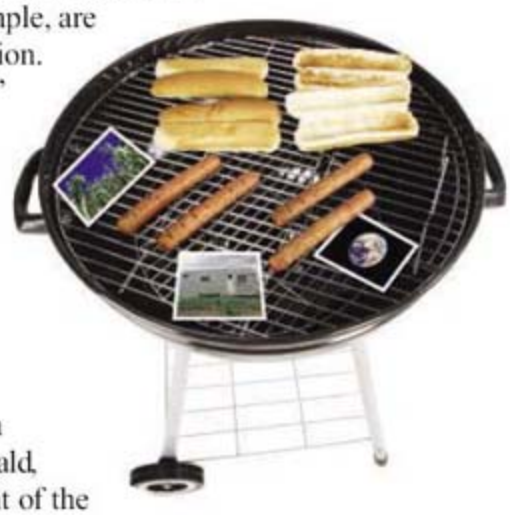
Donald Kennedy is Editor-in-Chief of *Science*.

Mixed Grill

EVERY ONCE IN A WHILE, IT'S GOOD TO LOOK BACK AT EVENTS—OLD ONES AND MORE recent—and see what has happened to them. Have things gotten better? Were there surprises? Did certain issues shrink and disappear, or others blossom because of an intervening event? Here, an informal checklist:

Science fraud. As far as we (*Science*) can tell, the incidence of research misconduct is neither up, nor down. The concerns raised by an advisory group that examined our handling of the Hwang case warned of an increase in competitiveness and incentive to overclaim or even cheat. Accusations may be more common, but we don't see enough serious incidents to convince us that competitive pressure has made the environment distinctly more inviting to fraud.

Animal activism. Last year, I said that animal activism was out of control (*Science*, 15 September 2006, p. 1541). It still is, at least here in the United States: Faculty members at the University of California, Los Angeles (UCLA), for example, are still being harassed, most recently by arson and other forms of intimidation. UCLA's acting chancellor called the fire-bombers of last fall "terrorists." I thought that was a righteous term and used it myself. For some reason, a *Nature* editorial (24 May 2007) called use of the term "unwise branding," identifying it as a "value judgment." Well, it strikes me that folks who leave firebombs on professors' porches might be entitled to a fairly adverse value judgment.



Secrecy and concealment. I've complained about policy-makers in the U.S. administration who suppress scientific results if they don't support a particular political objective. Although most attention went to the case of Jim Hanson at the National Aeronautics and Space Administration and a few others, a rich lode of new material is opening up. Julie MacDonald, deputy assistant secretary for Fish, Wildlife, and Parks at the Department of the Interior, may be the champion science-buster of them all. The department's inspector general revealed that MacDonald interfered regularly by bullying staff to change recommendations on endangered species habitat, exposing the department to litigation. She resigned abruptly, shortly before being called to testify before Congress. And in a different space, the Federal Emergency Management Agency (FEMA) learned that some of the agency's trailers occupied by Hurricane Katrina victims had formaldehyde concentrations 75 times the maximum recommended dose. What did the general counsel do? He advised employees not to initiate testing because it might "imply FEMA's ownership of the issue" and invite litigation. Representative Henry Waxman (D-CA), on learning this, pronounced it "sickening…an official policy of premeditated ignorance."

Energy and climate change. Nothing much is new on climate change (i.e., no palpable move toward emission controls). But on energy, as Congress breaks for the August dog days, troublesome issues will still need settlement when it reconvenes in September (Waxman remarked that he wanted "August never to end"). Of special concern is the energy bill the House passed on 4 August. Much about it is good: 15% of private electricity production must come from renewables, and there are incentives for energy efficiency and developing biofuels refining capacity. What's missing is a tough fuel economy standard. Speaker Nancy Pelosi (D-CA) hopes that won't matter, because the Senate bill does have one. Hmm. After the recess the bill goes to a conference, and on the House side, one expects John Dingell (D-MI), who hates fuel economy standards. Enjoy the show.

Biofuels. Something interesting has happened that I didn't quite realize when last visiting this subject (*Science*, 27 April 2007, p. 515). A major economic shift has arisen through the fusion of the agriculture and energy sectors by the biofuels craze. That's troubling. As incomes rise, the marginal demand for food falls off, but the demand for energy tracks income growth. So the inhabitants of rich countries, who don't spend much for food but like cars, are happy to turn corn into petroleum substitutes. That will raise world corn prices, adversely impacting the food-dependent poor in developing countries. My agricultural economics colleagues say that this could endanger the steady, decades-long drop in world food prices, exacerbating the already harsh inequity between North and South.

– Donald Kennedy

10.1126/science.1148943

BIOMECHANICS

No Skimming Allowed

Pterosaurs were flying reptiles and the first air-borne vertebrates; they dominated the skies from the late Triassic to the end of the Cretaceous, during the epoch of their relatives, the dinosaurs. On the basis of similarities in jaw structure, it has been suggested that several pterosaurs, including *Thalassodromeus* and the giant *Quetzalcoatlus* (with a wingspan of up to 15 m), could have fed by skimming in a manner akin to that of extant ternlike shorebirds (*Rynchops* spp.) Skimmers fly low over calm shallow water with the tip of their lower beak dipping beneath the water surface. Humphries *et al.* have used full-sized models of mandibles from *Thalassodromeus* and the modern skimmer *R. niger* to demonstrate that the pterosaur bill would have generated an order of magnitude more drag in traveling through the water. Modeling indicated that the energetic cost to a shorebird of flying with its beak in the water is almost prohibitive (~20% of the total cost of flight), and the authors suggest this levy might explain the rarity of the skimming life-style. The substantially greater cost for a pterosaur larger than 2 kg appears to exclude outright skimming as a possible means for procuring food. Furthermore, many of the morphological specializations to the head and neck seen in *Rynchops* are not found in pterosaurs of any size, including the ability to regenerate broken or abraded bill tips and the presence of a reinforced lower jaw. — GR

PLoS Biol. **5**, e204 (2007).

BIOMEDICINE

Timing is Everything

Cervical cancer is the second leading cause of cancer deaths in women, with more than 80% of these occurring in developing countries that have limited access to screening programs. Some strains of a sexually transmitted virus, human papillomavirus (HPV), play an essential role in the pathogenesis of this cancer. Newly developed vaccines directed against these oncogenic strains have shown promising results in clinical trials aimed at assessing their prophylactic activity—that is, their ability to prevent high-grade precancerous lesions or cervical cancer in women who had not been exposed to HPV before vaccination.

Hildesheim *et al.* have examined whether HPV vaccination can promote an immune response to HPV in women who are already infected with the virus. Such therapeutic activity had not been observed in animal studies of the HPV vaccines, but data addressing this question in humans are important for ongoing discussions of when and to whom the vaccines should be administered to maximize their benefits. In a study involving about 2000 HPV-positive women in Costa Rica who were monitored for 12 months, the authors found that HPV clearance rates—measured as cell-mediated immunity to the virus—were comparable in subjects receiving the HPV vaccine (specifically, the bivalent HPV-16/18 cervical cancer candidate vaccine) and those who had received a control vaccine directed against an unrelated virus. Although the long-term effects of the current HPV vaccines are not yet known, the apparent absence of therapeutic efficacy noted in this study reinforces the view that the optimal time to vaccinate is before the onset of sexual activity. — PAK

J. Am. Med. Assoc. **298**, 743 (2007).

IMMUNOLOGY

Wearing One's Own Coat

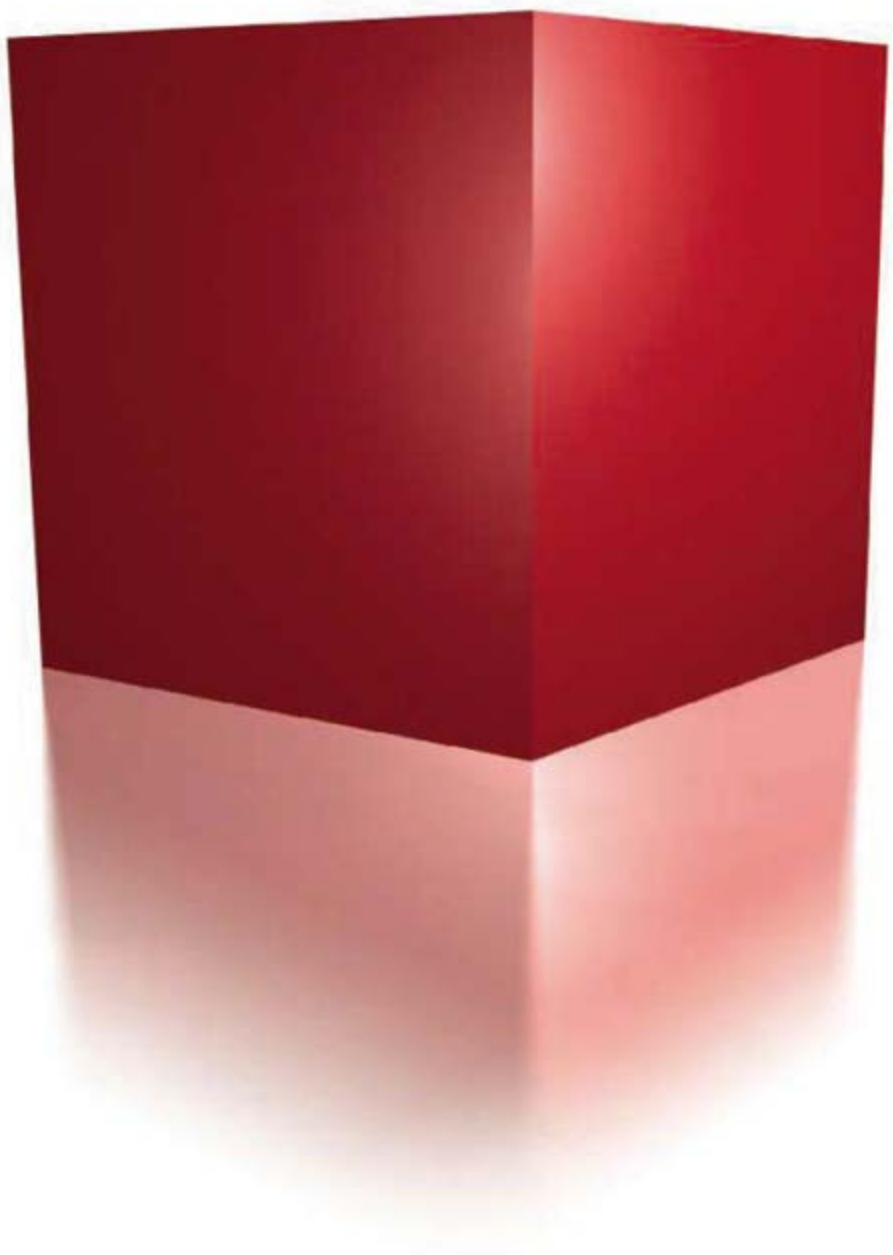
Autoimmunity conventionally falls within the realm of the adaptive immune system because it pertains to responses to self-constituents in humans and in a variety of animal models. Previous studies have shown that mice lacking the enzyme alpha-mannosidase-II (αM-II) exhibit a dearth of complex-type N-glycans and develop a syndrome similar to the human autoimmune disease systemic lupus erythematosus. Green *et al.* provide evidence that αM-II deficiency in mice involves activation of the innate immune system. The first piece of evidence emerged from the observation that initiation of disease did not require cells of hematopoietic origin; rather, the mesangial cells of the kidney were stimulated to produce inflammatory proteins. Subsequently, other cells of the innate immune system participated in the development of glomerulonephritis, which unexpectedly could be attenuated by boosting the adaptive immune system via injection of immunoglobulin G. The absence of αM-II resulted in a surfeit of hybrid-type N-glycans that were recognized by innate immune lectins otherwise dedicated to sensing the structurally similar mannose linkages of foreign glycoproteins. Future work might determine if the maturation of branched glycans on self-proteins broadly helps avert harmful innate immune responses, and whether pathogens might cloak themselves in complex-type garb as a means of evading detection. — SJS

Immunity **27**, 10.1016/j.immuni.2007.06.008 (2007).

Continued on page 1149

CREDITS: MARK WITTON

The shape of Life Science



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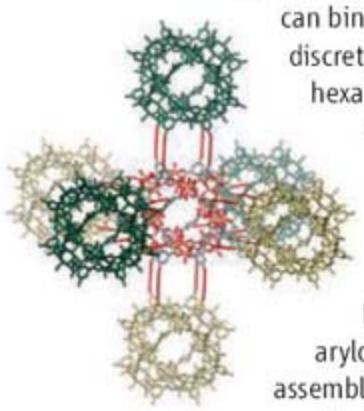
Continued from page 1147

CHEMISTRY

Networked Polyhedra

One approach to engineering porous solids has focused on combining metallic and organic building blocks. Linking multiple organic ligands to metal-ion nodes can produce microporous three-dimensional networks. In an extension of this method, small bidentate ligands such as 1,3-benzenedicarboxylate (bdc) can bind to Cu^{2+} ions to form discrete polyhedra (rhombihexahedra) that in turn act as larger nodes for assembling expanded networks. Perry *et al.* now show that when two bdc units are bridged with a flexible aryloxy spacer group, self-assembly with Cu^{2+} ions leads to a covalently linked set of the polyhedral units, arranged together in an interpenetrating tetragonal net. Crystallography reveals that the ligands adopt two independent conformations, one syn and one anti, in different directions within the lattice. — PDS



J. Am. Chem. Soc. **129**, 10076 (2007).

NEUROSCIENCE

Playing with Mirrors

Since the initial characterization of mirror neurons in the monkey—visuomotor neurons that fire during both execution and observation of movements—more than a decade ago, there has been much speculation about whether similar neurons in the human brain are involved in a wide range of social cognitive processes, such as understanding the emotions and intentions of others. Dinstein *et al.* point out that many of the human brain areas thus implicated were characterized as being active during imitation and have not always been shown to encode movements in a selective manner. Using brain imaging of subjects playing the rock-paper-scissors game, they describe a set of six cortical areas that were active during the observation and the execution of the three types of hand configurations, where selectivity was defined as a suppressed response to a repeated configuration (for instance, playing rock followed by rock). The same regions, in addition to a host of others, were active during imitation trials (simultaneous observation and execution) and also were active, albeit only weakly, during instructed movement trials—these two kinds of tasks having been used in most prior studies of human mirror neuron–like responses. One intriguing question raised by these findings is whether there might exist distinct, interspersed populations of visual and motor neurons within these regions. — GJC

J. Neurophysiol. **98**, 10.1152/jn.00238.2007 (2007).

CREDIT: PERRY *ET AL.*, *J. AM. CHEM. SOC.* **129**, 10076 (2007)

CLIMATE SCIENCE

Change in the Water

The rapid, millennial-scale cooling episodes (called Dansgaard-Oeschger events) that occurred repeatedly throughout the last glacial period are normally associated with climate change in the North Atlantic region. However, research over the past decade has also implicated their expression in the Pacific and Indian Oceans, leading to two competing explanations for the connection: atmospheric or oceanic transmission of the signal. Schmittner *et al.* used an ocean-atmosphere climate model to show that changes in buoyancy-forced ocean circulation can cause large variations in subsurface oxygen levels by changing oxygen demand. This result suggests that the climate signal of Dansgaard-Oeschger events originating in the North Atlantic was transmitted by oceanic, rather than atmospheric, teleconnections; further, it is consistent with the association of Dansgaard-Oeschger events with changes in the Meridional Overturning Circulation of the Atlantic Ocean. The influence of changes in wind stress and North Pacific Intermediate Water formation was also notable, though somewhat weaker than that of thermohaline circulation. Thus, ocean ecosystems and biogeochemical cycles appear to respond sensitively to ocean circulation changes. — HJS

Paleoceanography **22**, 10.1029/2006PA001384 (2007).

PHYSICS

Harmonizing High Harmonics

Intense infrared laser pulses can ionize the atoms of an inert gas and give rise to x-ray emission at high multiples (or harmonics) of the driving field frequency when the liberated electrons recombine with their parent ions. Selecting the output wavelength and boosting its intensity, however, have been experimentally challenging and have in large part been approached by trial-and-error. One severe problem is that the phase of emitted x-rays is out of kilter with the driving infrared laser field. Cohen *et al.* propose to address this issue by using a weak counter-propagating, quasi-continuous laser field to modulate the phase of the emitted harmonics. They show by simulation that tuning the wavelength of the counter-propagating laser field, and thus modulating the refractive index experienced by the driving field, could efficiently correct the phase mismatch. — ISO

Phys. Rev. Lett. **99**, 53902 (2007).

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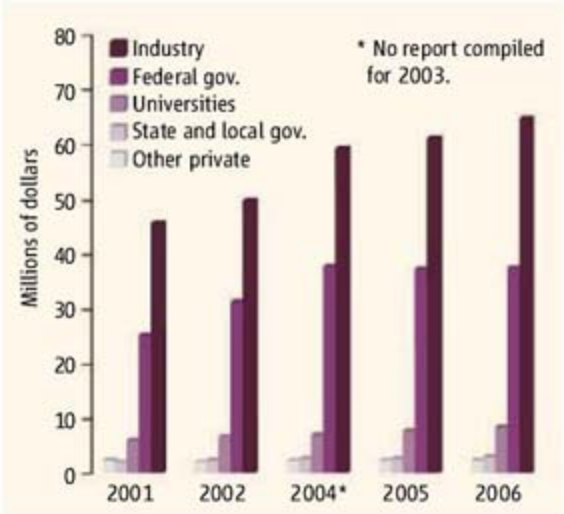
INFORMATION FOR AUTHORS

See pages 120 and 121 of the 5 January 2007 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

Health Research Funding: No Relief in Sight

Some policy wonks have suggested that foundations and other private sources will compensate for the flat National Institutes of Health (NIH) budget (*Science*, 11 May, p. 817). That's wishful thinking, says Research!America, a nonprofit group in Alexandria, Virginia, that tracks U.S. health research funding. Its latest analysis (below) shows that nonindustry private funding represented 2% of the $116 billion spent on U.S. health research in 2006 and has been "completely flat" since 2001, says Research!America policy analyst Stacie Propst.



Spending by industry has risen slightly since NIH's budget stalled at about $29 billion after 2004, but Propst predicts a dip because industry research funding typically follows federal patterns with a lag of a few years. The proportion of each U.S. health care dollar that now goes to research is 5.5 cents and falling, Propst adds; meanwhile, countries such as the United Kingdom and Singapore, although still behind the United States, are expanding their investments. "The trends are not good," says Research!America President Mary Woolley.

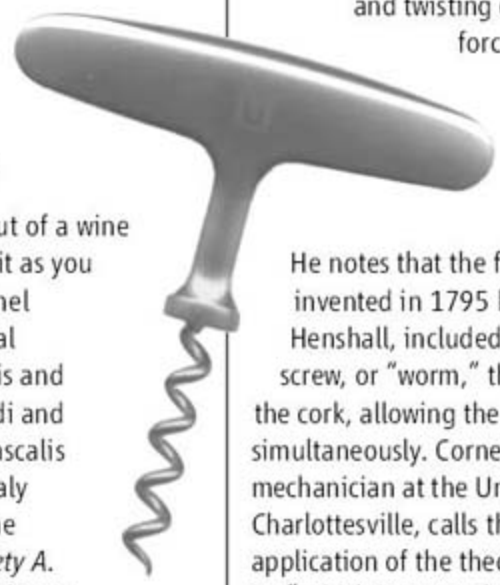
Filet of Zebrafish

NET WATCH

Long a favorite of developmental biologists, the zebrafish is now catching on with researchers studying cancer, drug addiction, and numerous other conditions. A new anatomical atlas for this scientific school is FishNet from the Victor Chang Cardiac Research Institute in Sydney, Australia.

The reference, which features 36,000 images captured using optical projection tomography, is the first to detail the fish's structure from embryo to adult. For each stage, visitors can call up lengthwise or cross-sectional slices, many of which include labels that pinpoint nascent organs and other features. Additional image sets highlight the developing nervous system and the skeleton. >>
www.FishNet.org.au

Crisp, With a Hint of Calculus



It's official: A cork will come out of a wine bottle more easily if you twist it as you pull. That's what physicist Michel Destrade of the French national research agency, CNRS, in Paris and engineer Giuseppe Saccomandi and mathematician Riccardo De Pascalis of the University of Lecce in Italy reported last week online in the *Proceedings of the Royal Society A*.

The team analyzed the problem to underscore that solids can deform in counterintuitive ways. For example, they show that a cork can twist internally even if it is pulled straight up. Such "secondary deformations" should not be overlooked, Destrade says. As a sidelight, the team also showed that pulling and twisting extracts the cork with less force than pulling alone.

That result won't surprise enophiles, says Rajendra Kanodia, proprietor of the Web site Corkscrew.com. He notes that the first patented corkscrew, invented in 1795 by Englishman Samuel Henshall, included a disk just above the screw, or "worm," that butts up against the cork, allowing the user to twist and pull it simultaneously. Cornelius Horgan, an applied mechanician at the University of Virginia, Charlottesville, calls the analysis "a very nice application of the theory of nonlinear elasticity," which is currently undergoing a renaissance with its applications to biological materials.

No Mean Cat Feat

Researchers working in central China have photographed one of the world's most poorly studied mammals, the Chinese mountain cat. First described by scientists in 1892, the cat (*Felis bieti*) is known only from a few skins in museums and six live animals in Chinese zoos, says Jim Sanderson, a mammalogist and founder of the Small Cat Conservation Alliance. In May 2003, Sanderson and colleagues Yin Yufeng and Drubgyal (his single Tibetan name) set out to find it in the wild. The effort paid off this summer, when their camera traps on the Tibetan Plateau in northwestern Sichuan Province caught eight photos of the cats hunting at night. Sanderson hopes the images will encourage conservation of the cat.

CREDITS (TOP TO BOTTOM): RAJENDRA KANODIA/CORKSCREW.COM; RESEARCH!AMERICA; J. SANDERSON

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EDITED BY YUDHIJIT BHATTACHARJEE

Three Q's

Chinese entomologist **Ren Wang** began his career studying how to boost yields by controlling crop pests with beneficial insects. Last month, he took on the job of increasing the productivity of the 15 independent institutes that make up the $450 million Consultative Group on International Agricultural Research (CGIAR). Wang, 52, had been deputy director of research at CGIAR's International Rice Research Institute in the Philippines.

Q: What are CGIAR's priorities for helping poor farmers?

Improving the productivity of staple crops, especially for unfavorable environments such as South Asia or sub-Saharan Africa. This is low-hanging fruit. We have drought-tolerant maize that could raise yields from 2 to 4 tons [per hectare]. How you manage the challenge of sustainability with this intensification effort—that's an urgent issue.

Q: How about climate change?

CGIAR's goal is to help farmers be prepared for unpredictable weather. Flood-resistant rice is just one example. Farming-systems research—rotation, for example, and [fast-growing] crop varieties—can influence millions of people and could change global agriculture.

Q: What are the major challenges facing CGIAR?

We will try to improve the efficiency of CGIAR and make ourselves more lean, … [but] we need more support. We need to mobilize and convince our investors that international agriculture research provides promising solutions.

CREDITS (TOP TO BOTTOM): IRRI; REED HUTCHINSON; LANL

MOVERS

GRABBING A KNIGHT. Northwestern University in Evanston, Illinois, has stolen away a star organic chemist from the University of California, Los Angeles (UCLA). J. Fraser Stoddart, who has pioneered a subfield devoted to manipulating interlocked rings and other mechanically linked compounds, will begin moving most of his 30-member team from UCLA's California NanoSystems Institute (CNSI) next month to Northwestern's new Center for the Chemistry of Integrated Systems.

A native of Scotland, 65-year-old Stoddart joined UCLA in 1997. He's the third-most-cited chemist of the past decade and was knighted by the Queen of England in January. Stoddart says CNSI has struggled to fund its ongoing operations after receiving generous initial support from the state. Northwestern, by contrast, has been buoyed by an influx of cash from licenses for pharmaceutical compounds.

"I'm sad. I like having him in L.A.," says James Heath, a chemist at the California Institute of Technology in Pasadena, who collaborates with Stoddart on molecular electronics research. "This is good for Northwestern. It's clearly a program on the move."

RISING STARS

A GOLDEN SUMMER. Sherry Gong, an 18-year-old from Exeter, New Hampshire, tied for first place at the China Girls' Mathematical Olympiad held in Wuhan in China's Hubei Province this month. It was the first time the United States had entered the competition, held annually since 2002. In July, Gong also participated for the U.S. team in the International Mathematical Olympiad held in Hanoi, Vietnam, which was won by Russia. Gong shared her top spot with Zhuo Chen of China.

Also this summer, Adam Hesterberg, a 2007 graduate of Garfield High School in Seattle, Washington, took home top honors in the individual competition at the International Linguistics Olympiad in St. Petersburg, Russia. The 64 high school contestants at the event, now in its fifth year, were asked to decipher the rules of unfamiliar languages such as Hawaiian, Tatar, and a Papua New Guinean language called Ndom guided by some samples and their English translations. Russian and U.S. squads tied for first in the team competition.

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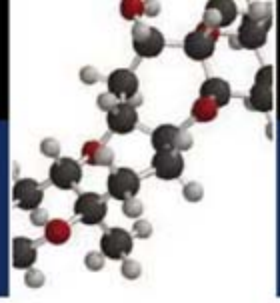
HONORS >>

AN OFFICER AND A SCIENTIST. In June 2006, Tod Caldwell went from studying how atomic decay affects metals at Los Alamos National Laboratory to Iraq's Anbar Province. It didn't take long for the reality of war to hit home for the physicist and U.S. Army sergeant first class. Three weeks into the reservist's deployment in Habbaniyah, a roadside bomb blew up a Humvee in his convoy, killing a marine. "I saw the vehicle flip over," says Caldwell, 39, who won a Bronze Star for, among other service, "personal courage" in securing the area and evacuating wounded soldiers. "It was a reminder that people wanted to kill you."

Caldwell, an intelligence officer, was stationed with an Iraqi army unit of 650 soldiers at a base for 8 months with no running water or food stores onsite. He took on the nickname "Sergeant Angry" for his direct style in training Iraqi soldiers. His technical side served him well when the bomb attack thrust him into the role of communications officer.

A prior stint in England in 2001 disrupted his Ph.D. research at Florida State University, which he completed in 2004. "It's frustrating in terms of my career," he says of his military service. But "it's rewarding to know what I've done."



A deadly ladder
1157

The pace of global change
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Cancer coalition. Flanked by cyclist Lance Armstrong and scientists, Texas Governor Rick Perry authorizes a $3 billion research fund.

CANCER RESEARCH

Texas Voters Asked to Approve $3 Billion Cancer Initiative

Texas is planning a biomedical research initiative fit for a state where everything is bigger: a $3 billion pot of money for its scientists to wage war against cancer. Legislation signed by Governor Rick Perry in June would create a cancer institute to manage the 10-year program, funded through state bonds. If voters approve the November ballot measure, the amount of money awarded annually will easily top the $226 million in grants that the state received last year from the National Cancer Institute (NCI).

Proponents expect the initiative to put Texas atop the world of cancer research and boost the state's biotech industry. "We want to be leaders in an area in which Texas is already very, very strong," says John Mendelsohn, president of the University of Texas (UT) M. D. Anderson Cancer Center in Houston, which this year was designated the nation's number-one cancer treatment center by *U.S. News & World Report* and which receives half of all the NCI money flowing into the state. But those high expectations won't be met, say scientists, unless the new institute selects the highest-quality proposals to support. Success will depend on a "top-notch peer-review process," says Alfred Gilman. Gilman is a Nobelist and dean of UT Southwestern Medical School in Dallas, another research powerhouse likely to benefit from the new grants program.

Scientists outside the state are applauding the plan, which has been endorsed by a coalition that includes the Austin-based foundation run by cycling champion and cancer survivor Lance Armstrong. "I think it's a very smart move on the part of Texas," says cancer biologist Webster Cavenee of the University of California, San Diego, who has watched California develop a similarly sized $3 billion initiative to fund human embryonic stem cell research. "It could be incredibly powerful, particularly if it were salted with a bunch of new people." And there are few dissenters. "It is not a popular position to complain," says Seth Chandler, a University of Houston law professor, who wonders whether it makes sense for the state to support cancer research, which, unlike stem cells, already receives substantial federal funding.

A friend of former governor Ann Richards, Austin business executive Cathy Bonner, came up with the idea of a cancer research initiative after the popular Democrat died last year from esophageal cancer. Bonner says she was aware of California's stem cell initiative and thought "now's the time" to do something similar for cancer research, which she felt needed a "big vision" in a time of flat federal funding. She joined with Armstrong's foundation and other groups and pitched it to Perry. By May, the legislature had voted to convert the state's cancer-prevention agency into the Cancer Prevention and Research Institute of Texas and to give it authority to fund scientific research on "all types of cancer in humans." Voters are being asked on 6 November to approve the sale of $3 billion in bonds to fund the institute, which would give priority to matching grants, those promising economic benefits, and collaborations. Up to 10% of the funds can be spent on prevention and 5% on facilities; the first grants would be awarded in 2010.

"This will be an enormous boost for cancer research in Texas at a time when federal funding has been very tight," says cancer biologist Jeffrey Rosen of Baylor College of Medicine in Houston. Mendelsohn hopes the money will encourage researchers to "do innovative things" in areas, such as nanotechnology, that are considered too risky for National Institutes of Health study sections and also attract new talent into the state.

The one concern raised by some scientists involves the fund's grants review committee. The legislation stipulates that half of the 18 members represent Texas schools, although they are nonvoting members to avoid potential conflicts of interest. Legislators wanted the schools to "have input into the process," says Ky Ash, a staffer for state representative Jim Keffer, the bill's House author.

The nine voting members must be either a physician or another professional who treats cancer patients, or represent a cancer treatment center or cancer volunteer group. Bonner expects most to be Texans because "we want to draw upon the expertise we have here" and says reviewers could include "retired doctors" and researchers at private cancer facilities.

That description makes some observers wonder about the panel's expertise. "You could end up with all of the voting members not really understanding much about research," ▶

CREDIT: MARGARET BOWLES/M. D. ANDERSON

A cancer conundrum
1160

Asian moon assault
1163

says Frances Sharples, a staff member at the National Academies. Several Texas scientists told *Science* they would much prefer that all reviewers live out of state. "There shouldn't be any Texans on the peer-review panel," says Michael Kyba of UT Southwestern, a reviewer for stem cell research initiatives set up recently in Connecticut and New Jersey that, like California's, draw reviewers from outside the state. Several others expressed similar concerns about the money being allocated on a political rather than scientific basis. "I would be greatly saddened if 5 years from now we're at an impasse because El Paso wants a cancer research center," says developmental biologist Luis Parada of UT Southwestern.

Mendelsohn suggests that the panel could tap outside researchers as needed to ensure high-quality peer review. Cavenee isn't worried about the limitations, either. "It will work out," he predicts.

Doug Ulman, president of the Lance Armstrong Foundation, says supporters will publicize the ballot issue and that such initiatives "typically do pass." Max Sherman, an emeritus political science professor at UT Austin, expects many to support it for a simple reason: Most families in Texas have been touched by cancer

–JOCELYN KAISER

PARTICLE PHYSICS

Fermilab Proposes Way Station on the Road to the ILC

Facing an uncertain future, officials at the last dedicated particle physics lab in the United States have developed a backup plan in case their grand ambition to host a gargantuan international collider were seriously delayed.

Under the plan, researchers at Fermi National Accelerator Laboratory (Fermilab) in Batavia, Illinois, would construct a proton accelerator using parts that meet all the design specifications for the proposed multibillion-dollar International Linear Collider (ILC). The proton source would feed neutrino experiments and searches for certain rare particle decays while serving as a test bed for the ILC, according to a draft report released by the lab's steering committee earlier this month. The more modest accelerator would still cost more than $500 million, and it faces competition from a Japanese lab.

Fermilab officials stress that their primary goal is to land the ILC. But that 40-kilometer behemoth, expected to cost more than $10 billion (*Science*, 9 February, p. 746), would require an international agreement that could take many years to hash out. "If things that are beyond the control of physicists are not ready, it would be much better for physicists in the U.S. to build a machine that is aligned with the ILC and gives you some real physics opportunities," says Fermilab Director Pier Oddone.

Dubbed Project X, the proton source would keep the lab on the research forefront during the period between the shutdown of Fermilab's Tevatron Collider at the end of the decade and the start-up of the ILC. The Tevatron will soon be eclipsed by the Large Hadron Collider (LHC) at the European particle physics laboratory, CERN, near Geneva, Switzerland, which will start smashing protons next year. Many physicists expect the LHC to blast out a slew of new particles. The ILC, which will collide electrons and antielectrons to make cleaner collisions, would be needed to study those particles in detail, researchers say.

Physicists hope to start building the ILC as early as 2012 and finish it by 2019. But in March, Raymond Orbach, under secretary for science at the Department of Energy (DOE), warned that the ILC might not be completed until the mid-2020s or later (*Science*, 2 March, p. 1203). Orbach asked the community for proposals that could be pursued in the meantime, and Project X is a response to that call, says Young-Kee Kim, deputy director of Fermilab.

CREDIT: FERMILAB

Priorities. Fermilab would build the proton source only if ILC were delayed, Director Pier Oddone says.

As early as 1994, some physicists had proposed building a proton source at Fermilab. But the previous design, called the Proton Driver, was seen as competing with the ILC, and in 2005 Fermilab put it on a back burner. The Proton Driver would have used some parts designed for the ILC, but Project X will use more of them and will stick to exact ILC specifications, says Tor Raubenheimer, an accelerator physicist at the Stanford Linear Accelerator Center in Menlo Park, California. "So in doing Project X, you really do advance the ILC," he says.

Fermilab is not the only lab with plans for a proton source. The Japanese Proton Accelerator Research Complex in Tokai should power up next year, although in its first phase it won't pump out as many protons as Project X would. Project X will also be measured against other midrange projects already proposed to DOE, including a space mission with NASA to study dark energy; experiments at the proposed Deep Underground Science and Engineering Laboratory, which is seeking funding from the National Science Foundation; and perhaps an accelerator to produce particles called B mesons in copious amounts.

Fermilab seeks $50 million over the next 3 years for research and development. Lab officials hope that DOE will come through with some money as soon as next year. The first step is a review by DOE's Particle Physics Project Prioritization Panel, which should weigh in next spring. **–ADRIAN CHO**

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ORGANIC CHEMISTRY

Synthesis Mimics Natural Craftsmanship

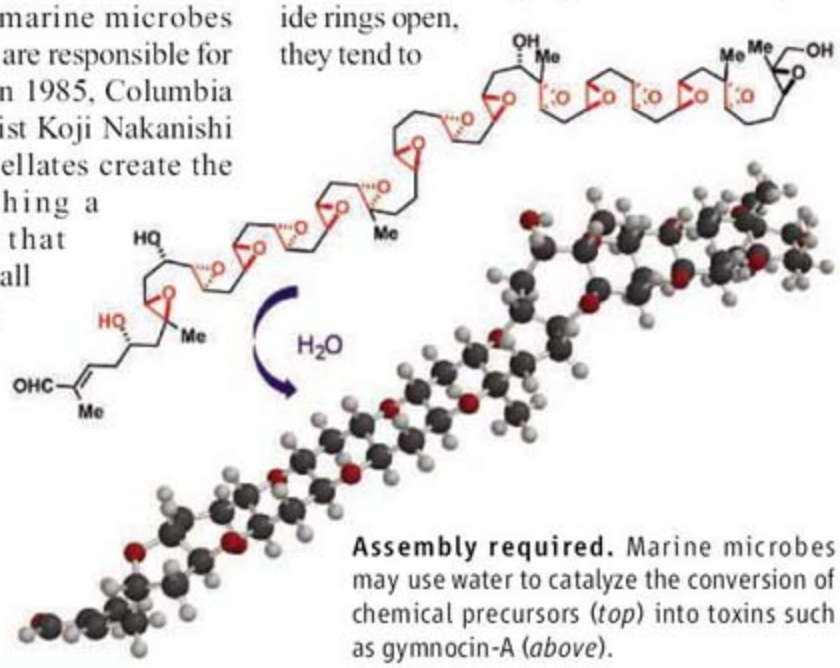
When it comes to making complex molecules, microbes are nature's master craftsmen. But just how they manage to construct some of these compounds has long remained mysterious.

Take a class of long, ladderlike toxins, such as those made by marine microbes called dinoflagellates that are responsible for fish-killing "red tides." In 1985, Columbia University organic chemist Koji Nakanishi suggested that dinoflagellates create the compounds by launching a cascade of reactions that break apart a series of small molecular rings as the first step to adding successive rungs to the ladder. The trouble is that synthetic chemists have never managed to create these cascades in water, leaving them to wonder whether it's truly the way the dinoflagellates do it. But now things may be looking up for this old idea.

On page 1189 of this issue, a team led by Tim Jamison, a synthetic organic chemist at the Massachusetts Institute of Technology (MIT) in Cambridge, reports that it produced just the sort of cascade that Nakanishi proposed. What's more, the MIT researchers found that the reaction actually works better in water—suggesting that waterborne marine microbes may build their deadly toxins in a similar way. "It's really a terrific result," says Eric Jacobsen, a synthetic organic chemist at Harvard University. The new work may make it far easier for chemists to craft new families of ladderlike compounds, some of which have shown promise for treating conditions such as cystic fibrosis.

Although complex, the ladderlike compounds have a recurring theme. Each is made up of a chain of small rings containing carbon and oxygen atoms. Some intersperse the occasional large ring or add different chemical appendages. After working out the structure of some of these compounds, Nakanishi proposed that dinoflagellates may create them by launching a series—or cascade—of reactions that open small ring compounds called epoxides, each of which contains an oxygen atom bound to two carbons. If the resulting compounds are put together right, the complex three-dimensional arrangement of bonds in the molecules would be in the right place and orientation. "It offers a simple way to explain a lot of complexity," Jamison says.

But there's a slight problem. When epoxide rings open, they tend to form one of two compounds. One, abbreviated THP, has just the right structure to become incorporated in a ladderlike compound; the other one, THF, doesn't. When chemists run their ring-opening reactions in organic solvents, they always get too much of the unwanted THF. They can bond additional groups to each epoxide to force it to react the way they want. But it appears nature doesn't do it that way.



Assembly required. Marine microbes may use water to catalyze the conversion of chemical precursors (*top*) into toxins such as gymnocin-A (*above*).

Intrigued by this puzzle, Jamison and his graduate student Ivan Vilotijevic dove in. After extensive work, they found a small ring-containing compound that, when placed in solution, seems to hold epoxides in just the right orientation to allow water to trigger the reaction. Not only does the reaction churn out THP, but that THP then primes another epoxide to break open and incorporate it into a growing chain. "It's so simple, and it opens up a lot of fundamental mechanistic questions about what water is doing," Jacobsen says.

The finding was heartening, Jamison says, because it suggests that dinoflagellates likely do something similar. In any case, Jamison and others say that the new reaction should make it much easier to create new ladderlike compounds that could pave the way for novel drugs.

–ROBERT F. SERVICE

CREDIT: I. VILOTIJEVIC AND T. JAMISON/MIT

SCIENCESCOPE

Slime for a Dime

Worm biology just got $4000 more lucrative. That's the amount a small team of leading worm biologists has put up for a reward to the first person to find a new sister species to *Caenorhabditis elegans*. The problem is that although the nematode *C. elegans* was the first animal to have its entire genome sequenced, the other nematodes sequenced since are too distantly related to allow biologists to identify the genetic differences in *C. elegans* that evolution has retained through natural selection. The worm's closest known relative branched off tens of millions of years ago, and scientists need a more recent relative for genome comparison.

Creators of the prize, including Caltech's Paul Sternberg and James Thomas of the University of Washington, Seattle, took a page from the Ansari X PRIZE—2005's $10 million private space flight competition—in announcing the prize, which will come out of their pockets. "Someone was talking about what types of species they would like to study," recalls Sternberg. "I whispered, 'I would pay 1000 bucks from my own pocket to see a true sibling of *C. elegans*.' James Thomas immediately replied, 'Me, too.' " Details are at Wormbase.org. **–ELIE DOLGIN**

Marvin the Martian, Googled!

Google Earth has been turned inside out. In partnership with three astronomical teams, Google has created a new feature for stargazers in its Google Earth interface. Dubbed Sky, the tool presents an easily manipulated map of the sky as seen from Earth, complete with constellations and the locations of famous images like the Pillars of Creation in the Eagle Nebula. Currently, images from the Sloan Digital Sky Survey and the Digital Sky Survey Consortium, along with about 125 of the best known Hubble shots, are the only ones displayed in the program, which is geared toward educational usage and the general public.

The astronomers behind the system, however, say Sky could in the future integrate more images from visible, infrared, ultraviolet, and x-ray observatories to make the system useful for academic scientists, either as a full-fledged reference system or as a way for researchers to do quick checks on areas of potential interest before consulting other professional databases. "Right now, that's a challenge," says astronomer Garth Illingworth of the University of California, Santa Cruz, who calls the tool a "great idea" for publicizing astronomy.

–BENJAMIN LESTER

CLIMATE CHANGE

Judge Orders More Timely U.S. Reports

A U.S. federal judge has rejected the Bush Administration's sluggish approach to reporting the results of its $1.7 billion climate-research effort. But even researchers critical of the government's climate-science program say it's a hollow victory for those seeking meaningful information on how global change affects the nation.

Last year, environmental groups led by the Center for Biological Diversity in Tucson, Arizona, sued the Administration, claiming that it had ignored a 1990 law that calls for "an assessment" of climate-change research every 4 years that "integrates, evaluates, and interprets" the latest research and describes its impact on the country. Noting that the government is nearly 3 years late in delivering such an assessment and 1 year late on a related mandatory research plan, Judge Saundra Brown Armstrong of the U.S. District Court for the Northern District of California rejected the Bush Administration's argument that the deadlines were flexible enough to allow the delays. "The defendants have not adhered to the text of the statute or its mandates," Armstrong wrote in her 21 August ruling, adding that the research plan should be released in March 2008 and the assessment in May.

Not surprisingly, the Administration and its opponents interpreted the decision quite differently. The White House science office says the new deadlines are "consistent with the Administration's current plans," although it is considering an appeal. But Senator John Kerry (D–MA) and Representative Jay Inslee (D–WA) say the ruling shows that officials have been "illegally suppressing" scientific facts and "crippling this country's ability to respond to the global warming threat."

Data drought? The White House is ordered to speed up its assessment of climate-change impacts.

At the same time, the judge did not address the planned form of the Administration's analysis, an issue on which she said Congress has not "clearly dictated." In 2000, the Clinton Administration summarized hundreds of studies on possible climate impacts in a 600-page report based on years of consultation with hundreds of scientists and local officials. In the place of this single, integrated report, the Bush Administration's interagency Climate Change Science Program (CCSP) has opted to write 21 shorter reports on various aspects of climate change, six of which it says fulfill the law's requirement. The first report was issued last year; a second one came out in June.

Richard Moss, who ran the climate change office under Bush until 2006, called it "unfortunate" that the ruling criticized the timing of the reports but failed to force CCSP to integrate its findings. "The Administration should be held to a higher standard than just what a judge finds follows the letter of the law," says Moss, adding that Americans deserve a "full soup-to-nuts national assessment" of how climate change will impact them. A bill that would force such an integrated approach passed the House of Representatives last month and is pending in the Senate.

–ELI KINTISCH

ENDANGERED SPECIES

U.S. Announces Recovery Plan for a Ghost Bird

Find them. That's the top priority in the effort to save the ivory-billed woodpecker, outlined in a draft plan last week by the U.S. Fish and Wildlife Service (FWS). But many critics fear that the charismatic bird is already extinct and worry that the $27 million plan will mean less money for conserving other endangered species.

Ivorybills (*Campephilus principalis*) were on the original federal list of endangered species in 1967. The last confirmed sightings of the large woodpeckers were in Louisiana in 1944. But in 2005, a team led by the Cornell Lab of Ornithology announced that it had evidence that at least one male was alive and flapping in Arkansas, a stunning claim that has since attracted vigorous skepticism (*Science*, 17 August, p. 888). Right after the announcement, FWS convened experts to figure out how to help the species bounce back.

The 182-page plan offers a detailed list of activities, many of which FWS is already either conducting or funding. The main task is to expand the search for the birds, now done mainly by a few academics, volunteers, and state wildlife agencies. Also high on the list are characterizing its habitat and developing computer models to project a healthy population size. These efforts, plus managing habitat, would cost $27.8 million over 5 years.

That price tag, in an era of scarce resources, makes some biologists shudder. "We put other species more at risk by focusing on a bird we can't find," says Louis Bevier, an ornithologist and research associate at Colby College in Waterville, Maine. FWS estimates it will have spent $1.1 million this year on the ivorybills, compared with a median expenditure in 2004 of $5500 per threatened or endangered species.

Chris Elphick of the University of Connecticut, Storrs, says the recovery plan gives short shrift to those who question the recent sightings in Arkansas. But FWS's Laurie Fenwood, who coordinates the recovery effort, says that the evidence was strong enough to compel the agency to act.

The plan is open for public comment until 22 October and will be reviewed by The Wildlife Society, a nonprofit scientific group in Bethesda, Maryland. A final version of the plan should be ready next year. And don't accuse FWS bureaucrats of negative thinking: If all goes well, the report says, the ivory-billed woodpecker could come off the endangered species list in 2075.

–ERIK STOKSTAD

CREDIT: ERIK RANK/GETTY IMAGES

AUSTRALIAN SCIENCE

New Misconduct Rules Aim to Minister to an Ailing System

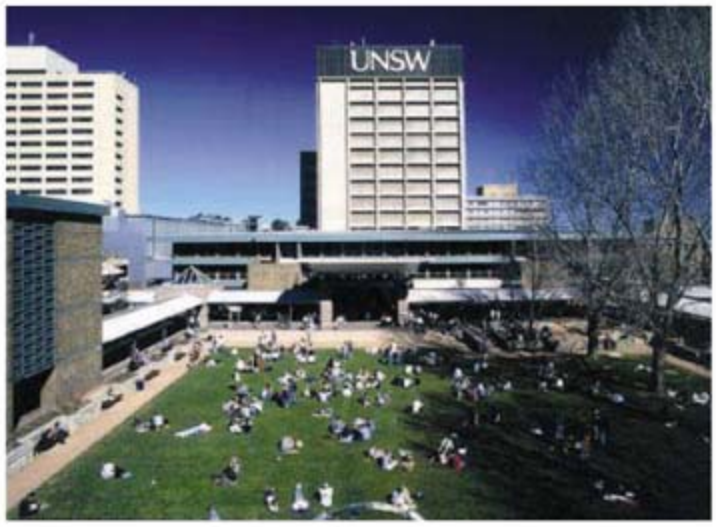
MELBOURNE, AUSTRALIA—Four years ago, a divisive series of investigations into the alleged scientific misconduct of a University of New South Wales immunologist bared what many scientists saw as a flawed system for handling such allegations. An external committee found the researcher, Bruce Hall, guilty of misconduct, but he retained his position after the university found him guilty of a lesser charge of academic misconduct (*Science*, 16 January 2004, p. 298). The case convinced the country's granting agencies and the community that changes were needed. The result, out this week, is a new code of research conduct.

"The code is a response to the train wreck of the Hall affair," says University of Sydney immunologist Robert Loblay. Warwick Anderson, chief executive officer of Australia's National Health and Medical Research Council in Canberra, which co-authored the new code, says it's meant to eliminate confusion over who should deal with alleged misconduct without being too prescriptive. "If there's a system everyone understands, things should work better," he asserts, adding that researchers should regard it as "a manual for good self-regulation."

The first part of the code lays down the rules of the road for professional duties such as mentoring students, handling questions about data and authorship, and interacting with industry. Part B offers a road map for when things go south. In the event of a "reasonable suspicion that research misconduct has occurred," according to the code, a potential whistleblower should report concerns to a designated university official. That official, typically a deputy vice-chancellor of research, would then choose an appropriate response, anything from declining to pursue the matter if the facts do not support the allegations to convening an external investigative panel. It's up to the university to mete out any punishment; funding repercussions rest with the appropriate granting agency.

The new code, unlike the current one adopted in 1997, covers work funded by the Australian Research Council as well as the health and medical council, extending its reach to all areas of basic research. It also removes scientific misconduct from a list of offenses, such as sexual harassment or embezzlement, that fall within an institution's enterprise bargaining agreement. That's an important change, as the bargaining agreement requires all problems to be handled by the accused person's immediate supervisor. In the Hall case, that was the dean of medicine, a person seen as potentially biased given that a finding of misconduct could damage the medical school.

Leaving the investigation in the hands of the home institution poses "an inherent and glaring conflict of interest" for institutions that fear adverse publicity, says Martin Van Der Weyden, editor of *The Medical Journal of Australia*. Loblay says that the accused would also benefit from the establishment of an external body to oversee investigations. "Hall had no one to complain to," he notes. Loblay and others believe that Australia needs an independent body like the U.S. Office of Research Integrity, and Anderson says "we are about to start exploring that."



Academic honor. Australia's new code of conduct provides a road map for researchers.

CREDIT: UNSW

In the meantime, one of those who initially accused Hall of misconduct is skeptical that the new code will make any difference. Juchuan Chen, a postdoc in Hall's lab who eventually took his concerns to the Australian media, says that the 4 years he spent on the case caused him to fall irretrievably behind in his research area and also ruined his reputation. "No one wants to hire a whistleblower," he says.

The new code will go into effect over several years as universities negotiate new 5-year workplace agreements with employee unions.

–ELIZABETH FINKEL

Elizabeth Finkel writes from Melbourne, Australia.

Ocean Observatory Wet Under the Ears

The final pieces of the National Science Foundation's Ocean Observatories Initiative (OOI) have fallen into place. Last week, the Woods Hole Oceanographic Institution in Massachusetts and Oregon State University joined the Scripps Institution of Oceanography and the University of Washington in receiving contracts to be the primary managers of what is hoped to be a 5-year, $331.5 million effort to establish coastal, regional, and global networks of anchored sensor buoys and underwater vehicles. The network will provide the first real-time measures of key parameters such as nutrient levels and currents. Current measurements are often taken once, not continuously, and in specific points throughout the ocean that may or may not be indicative of larger patterns in the sea. "We don't … really know what normal means," says Holly Given of the Joint Oceanographic Institutions, which is running OOI.

In addition to illuminating new trends in ocean conditions and wildlife, says James Bellingham of the Monterey Bay Aquarium Research Institute in California, the initiative "heralds the beginning of a push to better instrument the ocean's interior, which is an essential part of developing a better ability to observe and predict Earth's climate."

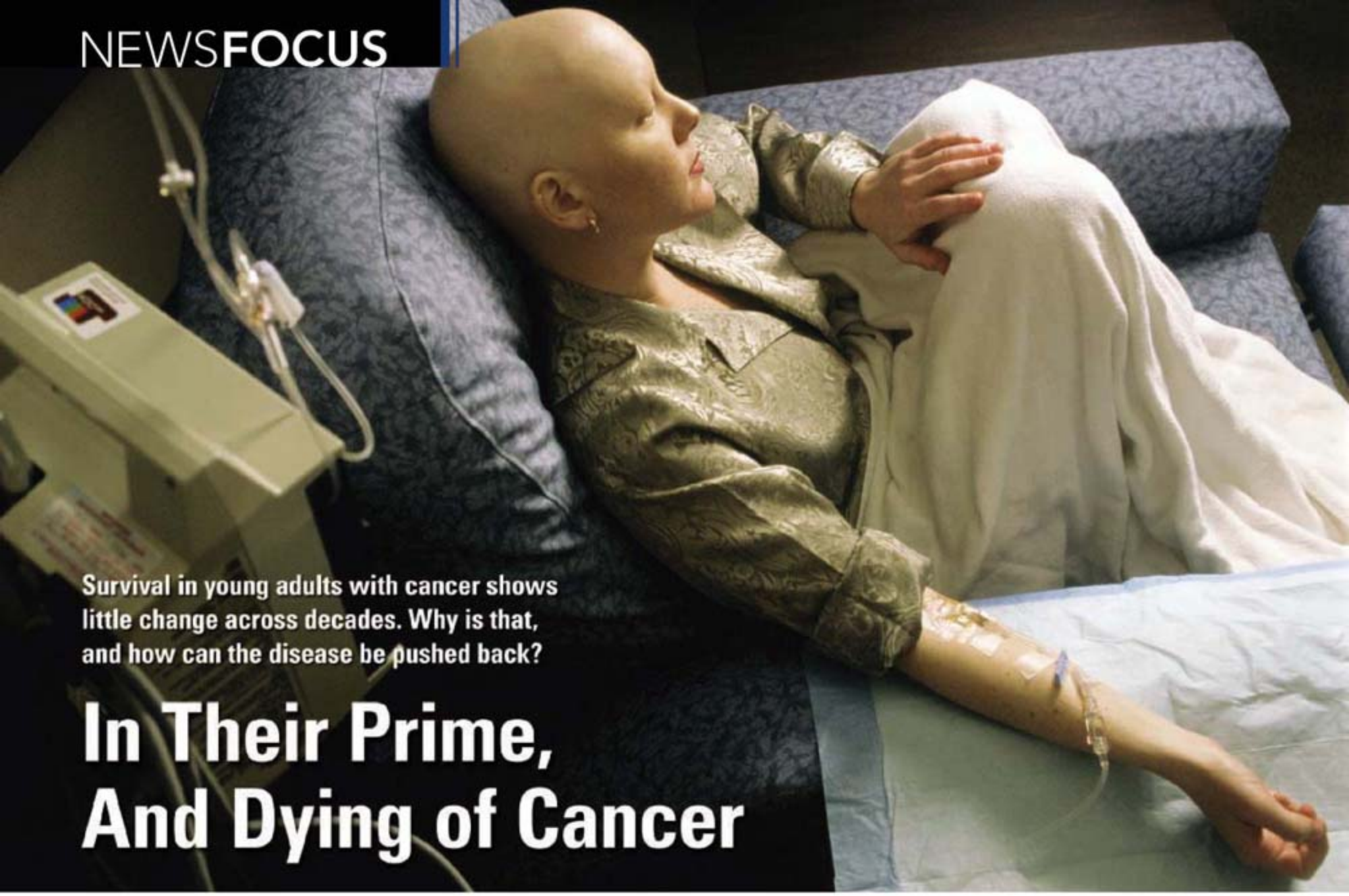
–MATTHEW BUSSE

Endangered Species at Issue

Political appointees have overruled scientists at the U.S. Fish and Wildlife Service (FWS) on endangered species decisions dozens of times, claims the Center for Biological Diversity (CBD) in Tucson, Arizona. This week, the environmental activist organization formally alerted the agency of its plans to sue, demanding it open an investigation of decisions made on 55 species.

FWS is currently reviewing eight decisions made by Julie MacDonald, a former political appointee with oversight of the agency. She resigned in May after the Department of Interior's inspector general found she had pressured scientists (*Science*, 6 April, p. 37). "The political corruption in the system goes way beyond eight species and Julie MacDonald," says CBD's Kieran Suckling. Among the cases he wants investigated is that of *Tabernaemontana rotensis*, a rare tree on Andersen Air Force Base in Guam. Agency scientists and peer reviewers concluded it deserved protection, but in 2004, FWS ruled it wasn't a valid subspecies and declined to list the species.

–ERIK STOKSTAD



Survival in young adults with cancer shows little change across decades. Why is that, and how can the disease be pushed back?

In Their Prime, And Dying of Cancer

THE NUMBERS STARED BETHANY Hartung bleakly in the face. Cancer survival rates in older adults and children had inched up an average of 1% or 2% each year over 2 decades, the graph showed. But for teenagers and young adults like her, the prospects for survival had barely budged.

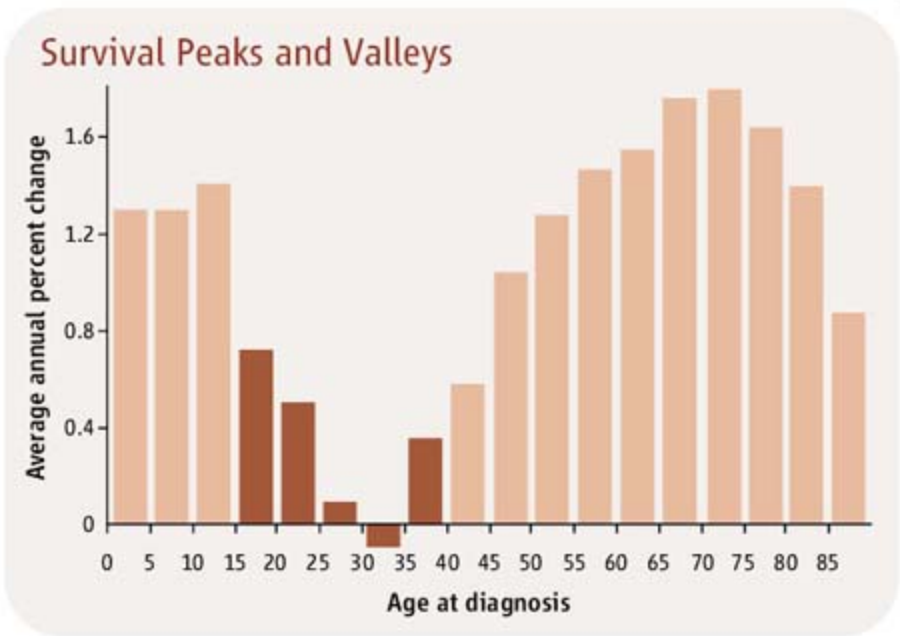
Remembering the moment she came across those statistics, "I was just kind of amazed," said Hartung, 21, in a telephone conversation from her family's home outside Portland, Oregon, 5 days before she died of leukemia. She had endured two relapses and nearly 3 years of grueling treatment, including a bone marrow transplant. When that failed to help, she was offered a spot in an experimental phase I study of a toxic therapy that she believed had little chance of beating back the disease. Hartung declined. "It was pretty much an easy decision," she said. Instead, she entered hospice care at home and died on 24 June, 2 weeks before her 22nd birthday.

According to data on age and risk, Hartung's chances would have been far better had she been diagnosed at 9 instead of at 19. Reversing her particular disease, acute lymphoblastic leukemia (ALL), is one of the great cancer success stories of the 20th century. In 1970, roughly 80% of children with the disease died; today, 80% will survive. But that heartening figure takes a dive in older teenagers and young adults, for whom 5-year survival hovers around 50%. No one knows exactly why.

The mystery extends well beyond ALL. Breast cancer, colon cancer, bone tumors, certain lymphomas, and Ewing sarcoma, which attacks bone and soft tissue, are all likelier to kill 15- to 39-year-olds than those in many other age groups. Adolescents and young adults (AYAs) with cancer once had better prospects than children and older adults. But their survival rates have been virtually frozen since about 1975.

The possible explanations are many and much debated. One is that therapies are not being designed for them because AYAs are poorly represented in clinical trials. Diagnosis often comes later, perhaps because of their aura of invincibility. In the United States, this cohort is less likely than other groups to have health insurance. Finally, their treatments may not be aggressive enough.

Some oncologists offer an altogether different explanation. "My own personal belief is that one part



Grim news, for some. From 1975 to 1999, the chance of surviving cancer for 5 years slowly improved in older adults and children but not for those in between.

CREDIT: KEVIN LAUBACHER/GETTY IMAGES; SOURCE: SEER

of this must be the distinctive biologies" of the patients or their tumors, says Michael Caligiuri, director of the Ohio State University Comprehensive Cancer Center in Columbus. He admits that laboratory proof is lacking, however.

Efforts to address this controversial idea are heating up. Researchers are beginning to assemble tissue banks dedicated to young adult tumors and looking for clues in the literature. This fall, after years of planning, one of the first clinical trials limited to 16- to 29-year-olds will examine the age group's lagging survival in ALL. And in the past 2 years, the Lance Armstrong Foundation in Austin, Texas, has poured nearly $2 million into the field and begun to reverse what is seen as years of neglect of AYA patients, whose U.S. ranks grow by nearly 70,000 each year.

"You see two patients who come in with what the pathologist tells you is the same disease, and you see drastically different outcomes" depending on age, says Caligiuri. "The onus is upon us to sort it out."

Knowledge gulf

Assembling the jigsaw puzzle will demand an alliance that extends across the boundaries of age—a rarity in medicine. "Biology doesn't change on a dime on the day of the 18th birthday," says Karen Albritton, who directs the Adolescent and Young Adult Oncology Program at Dana-Farber Cancer Institute in Boston. But the health-care and biomedical research enterprises act as though it does.

Albritton has experienced this cultural divide firsthand. From her residency days, she knew she did not want to choose between treating children or adults. But she recalls doctors telling her that working in both camps "would be combining things that don't combine."

That thinking is reflected in the paucity of data on the AYA crowd. In children, "we have great tissue banking for leukemia," says Leonard Sender, who directs adolescent and young adult cancer programs at Children's Hospital of Orange County and at the University of California, Irvine. "As soon as you go to 18, 19, 21," he says, the samples are "totally falling off."

Clinical trials, meanwhile, rarely include older teenagers and young adults. Roughly 30% to 50% of child cancer patients under 15 participate in clinical trials, whereas for adolescents and young adults the number hovers around 1% or 2%. (The comparable figure for adults 40 and up is about 3% to 5%.) Some trials have age limits that keep older teens from enrolling. Others are based at children's hospitals, where few young adults are treated.

Take Ewing sarcoma, which strikes bone and soft tissue. One large Ewing's trial of a new chemotherapy combination published in 2003 and led by oncologist Holcombe Grier at Children's Hospital Boston included 518 patients. Fifty were 18 or older. More than double that number were under 10. The average age at diagnosis with Ewing's, however, is about 15.

"We don't really have a focus on whether the treatments that we know work in children work in older age groups," says Australian oncologist David Thomas. Thomas directs the adolescent and young adult cancer program at the Peter MacCallum Cancer Centre in Melbourne, Australia, as well as the hospital's sarcoma genomics and genetics laboratory. Frustration shades his words as he talks about how poorly AYA cancers are understood. Even the most rigorously designed clinical trial will not detect AYA-specific differences in drug response or tumor biology, says Thomas, if only a tenth of participants are from this age group.

Data on young adults are also scarce because relatively few trials focus on the predominant tumors in this group: sarcomas, melanomas, thyroid cancer, gonadal tumors such as testicular cancer, and lymphomas. Some melanoma trials, which Sender notes already include few patients under 30, are ramping down because of tight federal budgets.

Before researchers began studying AYA patients with cancer, there was little awareness that survival rates were stagnant. Some studies did suggest that young adults with certain cancers, like sarcomas, were at a survival disadvantage compared with children—but it wasn't clear why. Albritton notes that she had treated older patients whose oncologists, unaccustomed to a cancer such as Ewing sarcoma that's more familiar to pediatricians, sometimes omitted chemotherapy. And a 2003 German study suggested that AYAs with Ewing's fare better in pediatric centers. Grier's clinical trial underscored that biology might also be key. Although the focus of Grier's trial was a new chemotherapy regimen in Ewing sarcoma, it contained some startling statistics. Treatment was standardized, yet the 5-year survival rate for children under 10 was 70%, compared with 60% for 10- to 17-year-olds and 44% for those 18 years and older. "We don't have any understanding" of why this occurs, says Albritton.

Fighter. Bethany Hartung (*center*), 21, celebrates Christmas last year with her older sisters. She died in June of leukemia.

CREDIT: PAM KRAMER

Behind the numbers

Several forces galvanized the cancer research community to dig deeper into AYA cancers. The first was a persistent campaign by W. Archie Bleyer. Trained as a pediatric oncologist, Bleyer worked for many years at the University of Texas M. D. Anderson Cancer Center in Houston before moving to St. Charles Medical Center in Bend, Oregon. Bleyer compiled and publicized the stagnant AYA survival statistics that astonished oncologists. Says Caligiuri of Ohio State University: "You look at [the numbers] and go, 'Oh my god, what is wrong here?' "

A second factor was an expanding advocacy community, led by the Lance Armstrong Foundation. Founded by the Tour de France champion who beat metastatic testicular cancer, the foundation joined with the National Cancer Institute to issue a set of "research and care imperatives" in 2006 and in May published a strategic plan for boosting AYA survival. The Lance Armstrong effort, called the LIVESTRONG Young Adult Alliance, is now led by 39-year-old Ewing sarcoma survivor Heidi Adams, who runs the advocacy group Planet Cancer, and oncologist Brandon Hayes-Lattin of Oregon

Health and Science University in Portland, who exhausted his arsenal trying to save Hartung. It will hold its second annual meeting in Austin in November.

Albritton, Bleyer, and many others are donating their time to one of its first projects, a literature search for clues about tumor biology. For example, a mention of young adults in a paper might prompt a call to the authors for additional data. "If there was a big breast cancer study but it lumped all the ages together, we go back to authors and say, 'Can you look at this by age?' " says Albritton.

Oncologists are also beginning to collect young-adult tumor samples that could be examined for chromosomal mutations and other characteristics. Sender, for example, hopes to gather melanoma samples, and Albritton is hunting for colorectal cancers in young adults. She has coaxed her Dana-Farber colleague, cancer geneticist Ronald DePinho, into analyzing the samples. DePinho believes that "there must be something intrinsically wrong with the cancer cells or the host" that makes young adults with colorectal cancer resistant to treatment.

Researchers believe their work could extend beyond AYAs. Just as findings in retinoblastoma, a rare pediatric eye cancer, opened the door to an entire cohort of tumor-suppressor genes, "sometimes the most interesting stuff is at the edges," says Albritton.

A few AYA tumor types have already yielded intriguing patterns. Preliminary data suggest that in Ewing sarcoma, tumors actually form in different parts of the body depending on age: in the extremities among younger patients and in the pelvic region in older ones, where the tumors are more difficult to remove surgically.

At the molecular level, there's growing evidence of a "mixing" of adult and pediatric patterns. In gastrointestinal stromal tumor (GIST), a cancer of the intestinal tract that is most common after age 40, a team at Memorial Sloan-Kettering Cancer Center in New York City 2 years ago described differences in a small sample of children, young adults, and older adults. Young-adult samples, they found, tended to blend qualities of both pediatric GIST, which usually lacks a classic gene mutation, and the adult form.

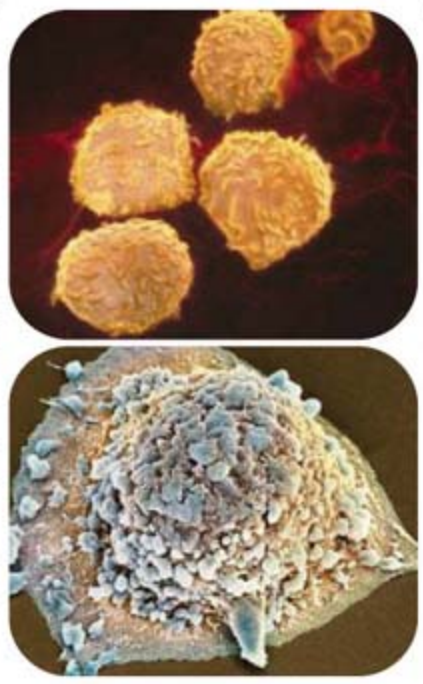
Rhabdomyosarcoma, which attacks soft tissue and is most common in children, shifts from an embryonic form in younger patients to an alveolar form in older ones. The distinction refers to the cells' genetics and appearance and where they congregate. Like many other pediatric cancers, rhabdomyosarcoma has a worse outcome in older patients, say oncologists.

Thomas is one of the few to focus on the AYA patient's biology. His recently completed study of 14,000 young Australians with various cancers revealed marked gender differences in AYAs. Young women over 15 were 80% more likely to survive than males if they had Ewing sarcoma, 40% more likely to survive if they had osteosarcoma, a bone cancer, and 50% more likely to survive with ALL. In youngsters under 15, gender did not seem linked to survival.

Seeking answers. Oncologist Karen Albritton wants to know why 20-somethings with sarcomas fare worse than children.

As far as he could tell, possible differences in male behavior—such as being less compliant in therapy—played no role, and Thomas concluded that the key to gender differences is puberty. For example, adolescent and young adult women have a higher percentage of body fat than males, which may affect the distribution of chemotherapy drugs; there may also be differences in drug metabolism. Thomas wonders whether the effective dose reaching tumors is higher for young females than for males. "Until we understand the biological differences" of the patient and the tumor, "we are not treating these cancers optimally," says Bleyer.

That's been evident since 2000, when Wendy Stock, director of the leukemia program at the University of Chicago in Illinois, presented new findings at a cancer meeting. She and a Chicago colleague, pediatric oncologist James Nachman, examined ALL trials conducted over the last 10 years by two cancer cooperative groups, one pediatric and one adult. Children, who can tolerate more intensive treatment, received a different chemotherapy regimen than adults, as is standard. Some AYAs were treated as children, some as adults, depending on which cooperative group they'd fallen into. Stock and Nachman examined the survival of 16- to 21-year-olds and found that those with ALL who enrolled in adult trials had a survival rate of 38%, about the same as older individuals. In the pediatric trials, their survival rate was 68%.



Distinctive? Scientists are wondering whether lymphoblastic leukemia (*top*) and colon cancer manifest differently in older teens and young adults than in other ages.

"Honestly, it was such a tremendous shock to us," says Stock. Researchers in France, Germany, and Italy subsequently reviewed their own ALL trials and encountered a nearly identical survival gap.

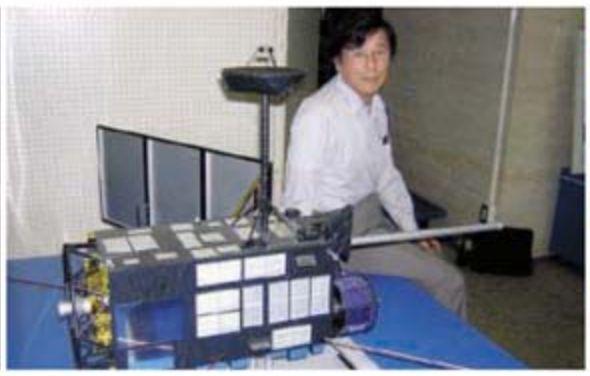
Oncologists floated several possible explanations, none reassuring. One is that they had been treating AYAs as though their bodies, and even their leukemia, were "adult" when really they were pediatric and ought to have received the regimen given to children. Another possibility is that the pediatricians, who encounter ALL more often than any other cancer, simply do a better job of treating it.

To learn more, Richard Larson, an oncologist who oversees clinical research in hematologic malignancies at the University of Chicago, is running an ALL clinical trial funded by the National Cancer Institute. It aims to enroll 300 16- to 29-year-olds starting this fall. Patients will be treated on a pediatric protocol by adult oncologists and will be compared with 16- to 21-year-olds with ALL in a separate ongoing trial who are receiving the same treatment from pediatricians. The key question, says Larson, is whether the survival rate can be linked to differences in a doctor's age-based specialty. The study is the first anyone can recall that focuses exclusively on young adults.

Meanwhile, the Stock and Nachman review has raised another troubling question: Have oncologists been undertreating adults across the board? With that in mind, Dana-Farber physicians are now experimenting with treating even adults up to age 50 with leukemia on a pediatric regimen.

Still debated is whether altering treatment will by itself erase the ALL survival gap. Sender believes that it's unlikely to be as simple as switching 30-year-olds to a pediatric regimen because "the leukemia has changed" fundamentally in these patients. Hartung's family will be raising funds to help uncover answers she did not live to see. Says her mother, Toni: "Her cause has become ours now." **–JENNIFER COUZIN**

CREDITS (TOP TO BOTTOM): DANA-FARBER CANCER INSTITUTE; GOPAL MURTI/PHOTO RESEARCHERS INC.; STEVE GSCHMEISSNER/PHOTO RESEARCHERS INC.


Over the moon. From left, China's Wu Ji, Japan's Manabu Kato, and India's G. Madhavan Nair are excited about upcoming lunar science missions.

CREDITS (TOP TO BOTTOM): PALLAVA BAGLA; D. NORMILE/SCIENCE; PALLAVA BAGLA

SPACE EXPLORATION

Asian Powers Shoot for the Moon With Orbiting Research Missions

They may not be in a space race, but China, India, and Japan are vying to make their marks on planetary science with first-time lunar missions

TOKYO AND NEW DELHI—If the moon shines more brightly on Asia in the next few years, it may be because three Asian powers are using a trio of spacecraft to shed some scientific light on the lunar surface. Barring last-minute glitches, Japan will launch its Selene mission on 13 September. China's Chang'e 1 is expected to go up within a few weeks of that launch, and India aims to follow in April with Chandrayaan-I.

Lunar scientists are cheering the science-driven missions, which promise the most detailed look at the moon since NASA's Apollo program. The results could help resolve outstanding questions about the moon's hazy origins and evolution and prepare for possible crewed landings. And although most data will be shared with European and U.S. colleagues, Asian scientists will be spearheading the analyses. "It's a good chance for Asian scientists" to make a mark in lunar studies, says Hitoshi Mizutani, a planetary scientist who led Selene's development until retiring 2 years ago from the Institute of Space and Astronautical Science (ISAS) in Sagamihara, Japan.

Lawrence Taylor, a self-proclaimed "lunatic" at the University of Tennessee, Knoxville, who is participating in India's mission, calls the upcoming season "an exciting time." He notes that NASA will be launching its Lunar Reconnaissance Orbiter (LRO) in late 2008. "The more enthusiasm we can generate [about lunar research], the better off we are."

For China, the moon mission is an opportunity to "make more contributions" to worldwide space efforts, says Wu Ji, a remote-sensing specialist at the Center for Space Science and Applied Research in Beijing. An indigenous space program is critical to India's future, notes G. Madhavan Nair, chair of the Indian Space Research Organisation (ISRO); this month, ISRO opened the Indian Institute of Space Science and Technology at Thiruvananthapuram, which will admit 120 students a year. Two decades from now, when space travel may become as routine as air travel today, Nair says, "we don't want to be buying tickets on other people's space vehicles."

On the science front, Selene's main aim is to provide the last word on the magma ocean hypothesis, a leading theory for how the moon formed, says Manabu Kato, an ISAS planetary scientist. The hypothesis holds that the early moon's surface was a molten mass several hundred kilometers thick that formed a crust as it cooled. This conception "is the best fit" for the characteristics of the 400 kilograms of moon rock samples that Apollo astronauts hauled back, Kato says. But those samples all came from mid-latitudes of the near side.

The long-delayed $458 million Selene, now also called Kaguya after a nationwide naming contest, will train 15 remote-sensing instruments on the moon from a distance of 100 km to determine the distribution of elements and minerals over the entire surface and to elucidate the moon's tectonic history. Putting all the observations together should reveal whether the magma ocean hypothesis holds up.

Surface mapping is a priority of the three missions. Scientists wonder whether most of the moon's craters were gouged in a brief period several hundred million years after the moon's formation, or whether the impacts tapered off over a much longer period. The extent and timing of the bombardment will provide clues to conditions of the early solar system. Three-dimensional surface imaging, which will help answer this question, is a key objective of Chang'e 1, which will orbit the moon for 12 months at a height of 200 km.

The star attraction of the $100 million Chandrayaan-I mission, meanwhile, is a probe that will plummet to the surface, snapping high-resolution images and measuring the sparse lunar atmosphere before crashing. The moon impactor is in part a technology test bed for future missions, says Madan Lal, deputy director of the Vikram Sarabhai Space Centre in Thiruvananthapuram, India.

Chinese researchers have been pushing for a lunar exploration program since the early 1990s, says Wu. But the government's priority was putting a person in space. In 2004, with the crewed program established, the center got a green light for three lunar missions. Chang'e 1, a $264 million effort, will be followed by a robotic lander in about 5 years and later by a sample-return mission.

India also sees Chandrayaan-I as a stepping-stone. ISRO is planning a rover mission in 2010, with a crewed effort possibly coming a decade later. China and Japan both developed the hardware on their own, whereas India collaborated with the United States and four European nations. Although Selene has no hardware from abroad, researchers from 15 countries are on the scientific teams and there is a data-sharing agreement with India. Wu says China didn't have time to find international collaborators, whereas India's Nair says he reached out for partners "to derive maximum scientific knowledge about the moon."

Many foreign scientists were glad to link arms with their Indian colleagues. "There are no opportunities [in Europe] to fly to the moon at present," says Stas Barabash of the Swedish Institute of Space Physics in Kiruna, who worked with colleagues at the Vikram center on a Chandrayaan-I sensor for imaging magnetic anomalies and surface composition. Similarly, NASA has no firm plans for anything after LRO. So with three probes ready to go and more being planned, Asia is offering scientists their best view of the moon.

–DENNIS NORMILE AND PALLAVA BAGLA

Trench warfare. Workers excavate the 6000-year-old mass burial beside Tell Majnuna, which lies in the background.

ARCHAEOLOGY

Murder in Mesopotamia?

Recent finds in Syria provide persuasive evidence that northern Mesopotamia rivaled the south in the race to build cities—and that it attracted enemies

Braving a trench filled with rat poison, archaeologists in Syria have found the remains of dozens of youths killed in a fierce confrontation nearly 6000 years ago—as well as evidence that the celebrating victors feasted heartily on beef in the aftermath. The researchers expect to find many more victims next year when excavations resume on a site that offers a rare window into violent conflict at a critical period of prehistory.

The surprising discovery is at the ancient site named Tell Brak, which scholars now believe was one of the world's earliest cities (*Science*, 9 June 2006, p. 1458). The 40-meter-high mound, located within sight of the Iraqi border in northeastern Syria, has been continuously excavated for more than 30 years but is only now revealing its surprising size and sophistication at this early age. Two papers published this week in *Antiquity* and *Science* lay out the case for a sprawling urban center in the 5th and 4th millennia B.C.E. rivaling contemporary settlements in southern Mesopotamia, long considered the undisputed birthplace of humanity's first cities.

A third paper—slated to be published this fall in the journal *Iraq*—will detail the mass burials at Tell Majnuna, half a kilometer north of the main tell at Brak. Local workers expanding a grain-storage facility last year were using bulldozers to cut into Majnuna—which means "crazy" in Arabic—and dig trenches, which they filled with rat poison to protect the grain. University of Edinburgh, U.K., archaeologist Philip Karsgaard investigated and spotted several layers of bone; this spring, Brak field director Augusta McMahon won permission from the landowner to excavate the site.

The first mass burial pit, on the western edge of the mound, has so far revealed the

Skull and bones. Jumbled burial at Majnuna may hold many more skeletons yet to be unearthed.

bones of at least 34 young to middle-aged adults, but only a small portion has been excavated. "There could be hundreds and potentially thousands," says McMahon, an archaeologist at the University of Cambridge, U.K. At least two skulls show signs of injuries that may have been the cause of death. The absence of feet and hand bones and the fact that many of the skulls apparently rolled off when the bodies were tossed into the pit hints that they were left to decompose before burial. On top of the skeletons was a mass of pottery, mostly vessels for serving and eating, and cow bones—evidence of a large feast.

A second mass burial pit is a dozen meters away, on the slope of the small mound, and appears to be from the same time. At least 28 individuals—also mostly youthful—were found in this burial, which includes clusters of long bones that may have been carried there by the armload. As in the first pit, there is a mass of pottery and cow bones, and fingers, hands, and feet are mostly absent.

A third area on the other side of the mound revealed a thick layer of ash more than 1 meter deep. It has yielded 13 skeletons of adults ranging in age from 20 to 45 and two children. Unlike the ones in the mass burials, these bodies appear to have been laid to rest carefully. The ages again hint at a violent death, but the pottery may come from a slightly later era; radiocarbon analysis results are not yet available, and McMahon says that all three areas have been only partly excavated.

McMahon says the site contains clear evidence of a violent confrontation. But she doesn't know whether the victors were defending or attacking Brak, or whether the feast commemorated victory or defeat. "We need at least another season to understand what happened," says Joan Oates, a Cambridge University archaeologist and Brak project director who began working on the site in the 1970s with her husband, David, who died in 2004.

From the pottery, Oates estimates that the Majnuna incident took place around 3800 B.C.E. She says Brak appears to have survived the confrontation and to have been destroyed 2 centuries later. After that event, influence from southern Mesopotamia begins to appear, and by 3400 B.C.E., southern pottery dominates the archaeological record.

Something similar took place at the nearby site of Hamoukar. Archaeologists from Syria and the University of Chicago in Illinois recently found evidence of a fierce battle at Hamoukar during the same period as the destruction of Brak, including hundreds of sling bullets, although archaeologists disagree whether they were actual weapons or had another use. In the past season, the Hamoukar excavators found a half-dozen burials from the period with a mix of genders and ages, although no obvious signs of violence are present. They also found a sling bullet lodged in a plastered wall, additional evidence that the bullets were weapons, says University of Chicago dig co-director Clemens Reichel. After the battle, residents appear to have

CREDITS (TOP TO BOTTOM): AUGUSTA MCMAHON/UNIVERSITY OF CAMBRIDGE

lived as temporary squatters amid the ruins; not long after, as at Brak, southern pottery appears. Both Oates and Reichel say this transition marks the demise of an independent northern Mesopotamian urban culture.

There are few examples of mass burials in the prehistoric Near East. The most dramatic is a pit found in 1997 at Domuztepe in central Turkey, containing the remains of nearly 40 people along with cattle, sheep, and goat bones, dating to 5700 to 5600 B.C.E. The victims, both male and female, range from infants to the elderly; numerous skulls show signs of fractures, and some skulls were chopped off. The human bones also show signs of burning, says dig co-director Elizabeth Carter of the University of California, Los Angeles, and cannibalism has not been ruled out.

A late-3rd millennium B.C.E. site called Titris Höyük in south central Turkey includes 19 skulls of mostly young men, with evidence of blunt-force trauma, but these are carefully arranged in an oval basin, says archaeologist Guillermo Algaze of the University of California, San Diego. Third millennium B.C.E. Mesopotamian texts describe similar scenes; the famous Stele of Vultures, for example, boasts of a Sumerian king heaping up corpses of enemies and depicts vultures carrying off their severed heads. The theme of victors celebrating a feast after a battle also is found in inscriptions of the era, adds archaeologist Glenn Schwartz of Johns Hopkins University in Baltimore, Maryland.

Brak was a thriving trade center and settlement both before and after the Majnuna incident. Working at the main mound in a deep cut, Oates and her colleagues recently unearthed evidence that the locals imported raw materials from hundreds of kilometers away and transformed them into manufactured goods in the 2 centuries or so before the mass burials. Researchers believe such a city might well have drawn the unwelcome eye of raiders or invaders.

Although lacking the drama of a battle or massacre, Oates's discovery offers an important glimpse into the era just before writing and large-scale urbanization transformed the ancient Middle East. The excavators uncovered several connected rooms dating to about 3900 B.C.E. and containing large piles of obsidian—a valuable volcanic glass used for cutting tools and obtained from distant Anatolia—along with imported jasper, marble, serpentine, and diorite stones used for beads. Also present was a large chunk of raw bitumen—the gooey substance that comes from eastern Mesopotamia—as well as mother-of-pearl inlay from local mollusks. Spindle whorls used for weaving wool littered the site, and a cache of 50 clay balls—either weapons or blanks for stamping ownership seals—lay in a corner of one room, its perishable container long decayed. "This is not household industry but a much larger institution," says Oates. "And evidence for industrial-based manufacture using imported raw material doesn't exist anywhere else" at or before this period, she adds.

The most unusual find was a chalice with a white marble base and black obsidian bowl held together at its seam with bitumen. The upper rim once contained another material, possibly gold, which was removed in antiquity. "We've not seen anything like this before," says Reichel. Found amid other coarser pottery, the drinking vessel, along with a stamp seal showing a lion being caught in a net—a classic Near Eastern symbol of royalty—suggests a well-stratified society in late 5th millennium Brak, adds Oates.

Drink up. This unique stone chalice was found in Brak's main tell.

CREDIT: JOAN OATES

An earlier building in the trench, which dates to about 4000 B.C.E., included large numbers of grinding stones, big ovens, basalt pounders, carefully crafted stone and bone tools, flint and obsidian blades, mother-of-pearl inlay, and clay spindle whorls. A street paved with pottery shards runs along the western side of the complex and to the city's northern gate. Part of the building and its street entrance remain buried under the high tell. The finds show an extraordinary continuity in manufacturing in a single area over a long period of time, Oates adds.

Brak's activity was not confined to the main tell. A close examination of the surrounding area reveals settlement in the period of 4200 to 3900 B.C.E. extending over an astonishing 55 hectares, an order of magnitude larger than other settlements of the time. During the first half of the 4th millennium B.C.E., Brak had more than doubled in size and its population density also increased. Only one city in southern Mesopotamia—Uruk—was likely larger in this era. And unlike Uruk, which was densely populated primarily in the center, early Brak appears to have featured various clusters of neighborhoods separated by open space. This more dispersed pattern, says Harvard University archaeologist Jason Ur in his report this week in *Science* (p. 1188), could show the existence of a less hierarchical social system than among the southerners.

The triple series of finds at the Brak dig, which is sponsored by the British School of Archaeology in Iraq, the British Academy, and Cambridge University's McDonald Institute for Archaeological Research, has drawn the rapt attention of other scholars. "It's absolutely unique and fantastic," says Algaze. "It is now clear that northern Mesopotamia is not the backwater people used to believe," adds Schwartz. With war in Iraq preventing exploration of the alluvial soil of the south, researchers are content to keep looking north for data on how the first urban centers coalesced.

–ANDREW LAWLER

Pea soup. Hans Paerl samples cyanobacteria in ailing Taihu Lake.

ECOLOGY

Doing Battle With the Green Monster of Taihu Lake

In attempting to subdue a vicious algal bloom, scientists aim to restore the health of a major lake in China and hone strategies for heading off toxic soups elsewhere

TAIHU LAKE, CHINA—As the motorboat glides through a carpet of fetid algae, Hans Paerl leans over the side and scoops up some of the tea-green muck with a plastic sampling bottle. In early June, a bloom of cyanobacteria, also called blue-green algae, fanned out across Taihu, China's third-largest lake. The growth was unchecked when a team led by Paerl, a cyanobacteria expert at the University of North Carolina, Chapel Hill, arrived last month to help colleagues at the Nanjing Institute of Geography and Limnology combat the foul bloom.

Much is at stake. Taihu, fed by the Yangtze River, helps irrigate millions of hectares of grains and cotton in a lush agricultural region between Shanghai and Nanjing. When it's healthy, the lake also provides drinking water for more than 2 million people, and it sustains one of China's most important fisheries for crabs, carp, and eels. The bloom that has turned Taihu into a toxic nightmare shows no signs of abating and may last until winter, experts say.

The ecological drama has far-reaching consequences. "It's safe to say that it's a pretty serious problem, and not just in China," says Paerl. At one time a villain largely confined to small lakes, algal blooms have of late gotten serious footholds in larger water bodies. Paerl warns that lakes such as Victoria in Africa and Erie and Okeechobee in the United States could be on the brink of becoming perennial algal soups.

That could pose a grave health risk. Some cyanobacteria, such as *Microcystis aeruginosa*, make toxins that can damage the liver, intestines, and nervous system. "Toxic cyanobacteria in drinking-water supplies pose a direct threat to public health," says Brett Neilan of the University of New South Wales in Sydney, Australia. Microcystis causes symptoms including diarrhea and liver failure. Reining in the algae at Taihu, Neilan says, could help prevent disasters elsewhere.

It wasn't long ago that Taihu enjoyed a cleaner reputation. A popular 1980s song, "Taihu Beauty," boasted of "white sails above the water, green reeds along the water, fish and shrimp below the water." Back then, says Paerl, Taihu rarely suffered blooms. Now they arrive like clockwork every summer, forcing locals to resort to bottled drinking water.

The root cause of Taihu's ills is an accumulation of nutrient-rich sewage and agricultural runoff in the shallow lake. That resulted in severe eutrophication: a surfeit of minerals and organic nutrients that nourishes algal growth. Unusually hot, dry conditions in early summer appear to have been the spark that ignited this year's bloom.

After the bloom reached nightmarish proportions 2 months ago, cleanup crews skimmed more than 6000 tons of algae from the lake and laid a polyvinyl chloride barrier to prevent algae from getting swept into pipes that funnel water to a drinking-water plant. But some organisms still seep through, says Qin Boqiang of the institute in Nanjing, and currents cannot flush away algae in water enclosed by the barrier.

Simply "cleaning out the algae" will not solve the problem, says Qin. He emphasizes the need to reduce nutrients, especially phosphorus and nitrogen, in the agricultural runoff and sewage. Paerl and Qin are conducting experiments to determine how much nutrient concentrations must fall to arrest a bloom. They also hope to unravel the dynamics of bloom formation. "The reason we developed this collaborative effort is that we have similar problems in the United States," says Paerl. "We thought, 'Why not combine our expertise?' "

Other researchers are probing the molecular biology of cyanobacteria toxins. With global temperatures rising, warmer surface water leads to less mixing, which favors the growth of toxic cyanobacteria. Deciphering the toxins' biological role and how the environment influences their production may suggest strategies for making blooms less venomous, Neilan says.

Cyanobacteria have a long history of acquiring remarkable adaptations, such as nitrogen fixation and gas vesicles that keep them afloat and enable them to outcompete diatoms and green algae for light and nutrients. They can lie dormant in extreme conditions—surviving droughts and freezing—then roar to life when conditions improve. Cyanobacteria are "very tough," Paerl says. "They're the cockroaches of lakes."

To control Taihu's little green pests, the government in the nearby city of Wuxi crafted an aggressive recovery strategy. The plan promulgates tough emissions standards for phosphorus and nitrogen for factories near Taihu and requires the installation of facilities that remove nutrients from sewage. Nutrient-rich agricultural runoff would be stemmed by banning chemical fertilizers, pesticides, and detergents that contain phosphorus or nitrogen. The amount of clean water pumped from Taihu is projected to reach 1 million tons per day by the end of 2008, and industries in Wuxi must meet a water-recycling rate of 78% by 2010.

"There's no doubt that Taihu is going to be a challenge," says Paerl. Degradation of the lake's water quality was a slow-motion train wreck that played out over several decades. It may take many more years to banish the blooms and bring back the Taihu Beauty of yore.

–LUCIE GUO

Lucie Guo is a freelance writer based in Boston.

CREDIT: HANS PAERL

EARTH MONITORING

Scientists Seeking New Homes For Orbiting Climate Sensors

Attempts to resurrect five sensors grounded by cost overruns on a suite of polar-orbiting satellites are confronting harsh budget realities

Free the NPOESS Five. That's the message from U.S. climate scientists hoping to find a way into space for five sensors stripped last year from plans for a multibillion-dollar satellite system (*Science*, 16 June 2006, p. 1580). An upcoming report lays out their preferences for salvaging the sensors, which are innocent victims of massive cost overruns in the $11 billion National Polar-Orbiting Operational Environmental Satellite System (NPOESS). But those choices—essentially, sticking the sensors back onto NPOESS or flying them on separate missions—are running up against tight budgets and a government decision to emphasize short-term monitoring for military and civilian weather forecasts over long-term measurements of global climate.

Conceived in 1994, the six-satellite NPOESS was envisioned as a joint military-civilian effort to provide weather and climate observations. But after $5 billion in cost overruns, a mandatory Pentagon review determined last year that weather forecasting would come first and that it could only afford four satellites over the next decade. The decision bumped five devices relevant to climate studies—an ocean altimetry sensor, ozone and aerosol sensors, and solar and terrestrial irradiation-detecting instruments (see chart).

Scientists complained about the resulting gaps in the climate record. So the two civilian partners—NASA and the National Oceanic and Atmospheric Administration (NOAA)—asked a panel of the National Academies' National Research Council (NRC) to review the agencies' options. The panel's report is expected shortly. Before its suggestions can be adopted, however, they will need to overcome fiscal and political realities beyond the scientists' control.

For starters, the triple alliance was supposed to make it easier to launch sensors that might not pass muster with an individual agency. But each partner has only so much to spend, and the overruns have taken their toll. "The more [money that agencies] use on the original project, the less you have for this additional effort," says NOAA atmospheric physicist W. Paul Menzel.

Despite tight budgets, NASA and NOAA officials have rough plans for launching additional satellites in 2014 and 2020. But the $1.1 billion cost per launch is said to be distasteful to White House officials, who declined comment. A third option—getting the data from Navy satellites or from foreign partners—depends on their ability to deliver high-quality data.

MEET THE NPOESS FIVE

SENSOR	MISSION
1. Total Solar Irradiance Sensor (TSIS)	Measures the energy of the sun's rays
2. Earth Radiation Budget Sensor (ERBS)	Monitors the radiation emanating from Earth
3. Ocean Altimeter (ALT)	Measures sea level
4. Ozone Mapping and Profiler Suite (OMPS-Limb)	Provides a detailed look at atmospheric ozone
5. Aerosol Polarimeter Sensor (APS)	Measures dust and other aerosols

A bird in hand. The CERES radiation sensor, already built, could stand in for ERBS, one of the five canceled sensors.

CREDIT: NORTHROP GRUMMAN

Although it removed the sensors, the Defense Department didn't shrink the size of each NPOESS satellite. That leaves "empty seats on the bus," says Menzel. But getting a ticket to ride has so far proven difficult. In January, a joint NOAA/NASA team suggested restoring some sensors to the first full NPOESS craft, dubbed Charlie 1, to be launched in 2013. But NPOESS managers later "froze" the plans to reduce the potential for technical glitches. White House officials may ask the managers to revisit that decision, because adding payloads to existing missions would be much less expensive than flying additional missions.

Scientists say that one of the sensors, the Ocean Altimeter, would actually be more valuable if flown on another satellite. (Climate researchers interested in altimetry were "never happy about being on NPOESS," says NOAA's Jeffrey Privette.) A higher and, therefore, more stable orbit would allow the instrument to take more accurate measurements of the minuscule increases in sea level. Scientists are now huddling with the Navy on a possible standalone altimetry satellite mission for 2013 or later, although the Pentagon's less stringent weather requirements may make it indifferent to pleas for greater accuracy.

Getting into space as soon as possible is crucial for one of the bumped instruments. The Total Solar Irradiance Sensor (TSIS) measures the total solar radiation bathing Earth, as well as the strength of various portions of the sun's rays, to help scientists monitor trends in the sun's output. A NASA satellite began collecting those data in 2003, but Privette says he sees little chance of avoiding a gap between 2010 and 2014. The problem is complicated by the need for overlapping missions to calibrate the sensitive instruments.

Hitchhiking onboard other crafts could be the answer for other sensors. The Aerosol Polarimeter Sensor might fly on Glory, a NASA craft set for launch next year whose solar-radiation sensor should maintain the continuity of TSIS's measurement record. And instead of the planned Earth Radiation Budget Sensor, which tracks energy radiated back from Earth, officials could deploy the already-built CERES on a 2010 NPOESS test mission.

The NRC report will also review the status of sensors still on the flight schedule. Reducing the fleet of satellites from six to four, for example, means that each spot on Earth will be covered twice rather than three times a day. The loss of a midday view means the Visible/Infrared Imager/Radiometer Suite won't see midmorning fog or clouds. That's unfortunate, as a big part of its mission is to document cloud patterns. A more limited scanner on a European weather mission launched last year is helping to fill the midday gap.

Privette has learned to cope with the steady stream of requests from scientists to influence payload plans. "Everybody wants something," he notes. But the uncertainties surrounding NPOESS may require him to fine-tune those coping skills.

–ELI KINTISCH

LETTERS

edited by Etta Kavanagh

The Risks and Advantages of Framing Science

THE POLICY FORUM "FRAMING SCIENCE" BY M. C. NISBET AND C. MOONEY (6 APRIL, P. 56) argues that because different audiences respond differently to certain science-based public policy issues, scientists should trade their reliance on fact-based arguments for ones more slanted toward the interests of specific groups. Their examples—climate change, evolution, and stem cells—seem all too similar to the parable of the blind men and the elephant, each man describing the beast differently based on his own limited data. In the end, although each describes a portion of the elephant accurately, none can picture the entire animal. That seems more a model for politicians than scientists, and Nisbet and Mooney's advice that "scientists should strategically avoid emphasizing the technical details of science when trying to defend it" seems somewhat dishonest. I would hope that researchers continue to rely on their data, rather than on what "spin" on an issue might prove more convincing.

EARLE M. HOLLAND

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The Risks and Advantages of Framing Science

THE POLICY FORUM "FRAMING SCIENCE" BY M. C. NISBET AND C. MOONEY (6 APRIL, P. 56) argues that because different audiences respond differently to certain science-based public policy issues, scientists should trade their reliance on fact-based arguments for ones more slanted toward the interests of specific groups. Their examples—climate change, evolution, and stem cells—seem all too similar to the parable of the blind men and the elephant, each man describing the beast differently based on his own limited data. In the end, although each describes a portion of the elephant accurately, none can picture the entire animal. That seems more a model for politicians than scientists, and Nisbet and Mooney's advice that "scientists should strategically avoid emphasizing the technical details of science when trying to defend it" seems somewhat dishonest. I would hope that researchers continue to rely on their data, rather than on what "spin" on an issue might prove more convincing.

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NISBET AND MOONEY'S PRESCRIPTION OF framing falls short of a comprehensive diagnosis and treatment plan for what ails science. The authors correctly argue that framing is one, albeit of many, powerful communication tools potentially useful to scientists. However, using framing for persuasion, political communication, or public relations ends does not necessarily empower people to make better decisions about complex issues (*1*, *2*).

The authors' argument may inadvertently perpetuate two commonly encountered science communication myths. The first is that complexity cannot be successfully communicated (*2*). The second is a counterproductive "two communities" notion that blames the public as eternally deficient and alienates science from society (*3*, *4*). Nisbet and Mooney can claim this misrepresents their intent, but that illustrates the inherent vulnerability of even a well-intended frame to differing interpretations (*5*). For instance, readers of *Science* may interpret the authors' advice to strategically sequester the "technical details of science" as equating framing with "dumbing down" science, even though Nisbet and Mooney certainly recognize that framing and technical complexity are distinct elements of language and communication.

Finally, what framing strategy wins the daily mass media wars may not enhance long-term relationships between science and society. Toward that end, evidence indicates that scientists should engage in more and ongoing dialogue with policymakers and the public to help build shared understanding and effective policy solutions (*1*–*4*, *6*). As Irwin wrote, "The relationship between science and society should not be about the search for universal solutions and institutional fixes, but rather the development of an open and critical discussion between researchers, policymakers and citizens" (*3*). At stake are not only relevance and increased adoption of science, but also long-term support for science, social cohesion and equity, trust, and well-being (*1*–*4*, *6*).

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IN THEIR POLICY FORUM, NISBET AND MOONEY assert that scientists need to become adept at communicating their science in public using frames "to make it relevant to different audiences." Although I agree, suggesting that scientists accept and use popular frames presents certain risks.

First, many scientists would prefer to "stick to the facts" in public for very good reasons. Frames are much more than simply "leaving out details," reducing jargon, or providing more context. When speakers frame "the problem of climate change as a matter of religious morality," for example, they are using science to support a philosophical argument. Scientists are reluctant to use frames like this one, not because of the details they have to omit, but because of the details they have to add. It's philosophy, not science.

Second, although others have used science in "foreign" frames to shape public opinion, when they dominate science media, important ideas are entirely absent. Frames work because they distill complex issues and emphasize what the audience already knows to be true. But we should be concerned if the dominant frames in the media omit the authoritative basis of science in empirical observation, experimental methods, and rational argument, for example. We're left with science "facts" in an alien frame. Without these concepts, how can society cope with scientific controversy or the implications of new and challenging discoveries?

Despite these drawbacks, "foreign" frames are important, and more scientists should

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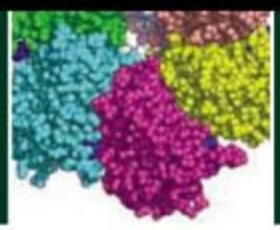
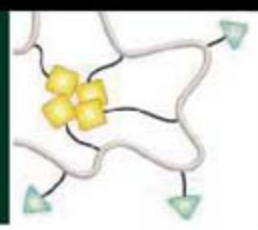


DNA, unwound

1181



Polymer drugs

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learn to use them. It is perfectly reasonable and legitimate to use emotional, religious, political, and economic metaphors, stories, and messages to frame science. Scientists are also citizens and have a right—even a responsibility—to frame their science in their own voices. Framing science in these ways does make science more accessible. But it's important to understand the risks of saturating the media with these popular frames, as well as the potential rewards.

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NISBET AND MOONEY ARGUE THAT "WITHOUT misrepresenting scientific information on highly contested issues, scientists must learn to actively 'frame' information to make it relevant to different audiences."

I would argue that framing the debate will lead to (i) having to misrepresent scientific information or (ii) sacrificing scientific credibility, both of which will only reduce the public acceptance of what science has to say.

For example, the authors say that the United Nations Intergovernmental Panel on Climate Change (UNIPCC) has "steadily increased its confidence that human-induced greenhouse gas emissions are causing global warming. So if science alone drove public responses, we would expect increasing public confidence in the validity of the science, and decreasing political gridlock." However, this would be true only if UNIPCC is seen by the public as solely presenting technical complexities as matters of science.

UNIPCC framed itself as a political institution seeking not just scientific conclusions, but acceptable social, economic, and political solutions. Because of this, critics can easily attack UNIPCC's scientific credibility as being influenced by a political or social agenda. As a result, we have decreasing public confidence and increasing political deadlock. Had UNIPCC stuck exclusively to the science, the public would have been far more receptive to the findings of the organization and critics would be much less able to dismiss UNIPCC's science as politically or socially motivated.

Science has credibility with the public precisely because the public believes that science is neutral, that it doesn't take positions or adopt particular frames. If we are going to adopt a strategy of adopting frames when communicating to the public, we should at least consider the possibility of the unintended outcome of sacrificing scientific credibility in the process.

Another example presented is the public debate concerning evolution versus creation. According to Nisbet and Mooney, "antievolutionists promoted 'scientific uncertainty' and 'teach-the-controversy frames,' which scientists countered with science-intensive responses. However, much of the public likely tunes out these technical messages. Instead, frames of 'public accountability' that focus on the misuse of tax dollars, 'economic development' that highlight the negative repercussions for communities embroiled in evolution battles, and 'social progress' that define evolution as a building block for medical advances, are likely to engage broader support."

Although not quite a public debate, recent events in Dover, Pennsylvania, and the findings of Judge Jones came close. The antievolutionists lost.

I think one reason why is that the creationists adopted "scientific uncertainty" and "teach-the-controversy frames" while science and evolution refused to adopt any frame at all. Those representing evolution made no appeals to "public accountability" or "economic development" implications. Rather, they stuck to the science. In so doing, they built their arguments on a rich intellectual tradition that, more than any other in our society, is seen as unbiased and credible. Ask any trial lawyer: The jury buys the testimony of the most credible witness. So does the public.

In contrast, those testifying for the antievolutionary camp were tainted. They destroyed their own credibility and diminished the power of any countering arguments.

The authors observe that "many scientists not only fail to think strategically about how to communicate on evolution, but belittle and insult others' religious beliefs." I have witnessed quite the opposite. The scientific community has been much too respectful of the religious beliefs of others. When someone claims that the world is 6,000 years old, that is belittling and insulting the work of science, and just plain dumb. Scientists have to say that, and say it more often.

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Response

IN SPINNING OUR SUGGESTIONS AS "DISHONEST," Holland assumes that framing is absent from traditional science communication. Yet, whether writing up a grant proposal, authoring a journal article, or providing expert testimony, scientists often emphasize certain technical details over others, with the goal of maximizing persuasion and understanding across contexts (*1*). Moreover, press officers and science reporters routinely negotiate story angles that favor particular themes and narratives (*2*) or, at the expense of context, define news narrowly around a single scientific study (*3*).

When attention to science shifts from the science pages to other media beats, new audiences are reached, new interpretations emerge, and new voices gain standing in coverage. These rival voices strategically frame issues around dimensions that feed on the biases of journalists, commentators, and their respective audiences (*4*). If scientists do not adapt to the rules of an increasingly fragmented media system, shifting from frames that only work at the science beat to those that fit at other media outlets, then they risk ceding their important role as communicators.

In response to Pleasant, we agree that a well-informed public is an empowered public. The problem, however, is that the availability of scientific information in the media does not mean people will use it. Only by framing issues in a manner that makes them personally meaningful and accessible to nontraditional audiences can scientists and their organizations boost public attention and thereby sponsor informal learning (*5*).

We also agree with Pleasant that the type of dialogue featured at deliberative forums and community meetings remains important. Unfortunately, at these forums, the citizens

who are most likely to attend and speak up are those who are already informed and active on an issue (*6*). In contrast, carefully framed media presentations can effectively promote dialogue and trust with a larger and more diverse audience.

Consider, for example, E. O. Wilson's *Creation: An Appeal to Save Life on Earth* (*7*). By recasting environmental stewardship as not only a scientific matter, but also one of personal and moral duty, Wilson has generated discussion among a religious readership that might not otherwise pay attention to popular science books. A second example is Karen Coshof's documentary *The Great Warming* (*8*). Narrated by Keanu Reeves and Alanis Morissette, the theatrical release combines interviews of climate change experts with testimonials from religious leaders. Endorsed by national religious organizations, forums featuring the film have also been hosted by churches and synagogues. In addition, both of these examples function as news pegs for journalists at religious media outlets to write stories about climate change, thereby facilitating exposure among nontraditional audiences.

Contrary to Quatrano's warnings, in neither the Wilson nor the Coshof examples does science appear to support a particular religious philosophy or argument. Instead, framing is used to create a narrative bond between scientists and religious citizens, communicating a shared interest in what science can tell us about the nature of environmental problems.

In response to Gerst, scientists and their institutions are motivated to discover what is true about the world and to inform the public about the implications of their research. In translating this knowledge for popular consumption, should scientists rely solely on their instincts and their personal experience, or should they rely on a systematic understanding of communication? Applying research about the public and the media will only help the scientific community tell the truth more effectively and to a wider audience.

Framing is not all-powerful, nor should it be considered a magical key to unlocking public acceptance. Research on framing suggests that establishing a connection with audiences derives from the fit between the frames embedded in a media message and the interpretative schema that a particular audience possesses. One common source of science-related schema are long-term socialized world views such as political ideology, partisanship, ethnicity, or religious belief. Other sources are the stereotypes, narratives, and images learned through popular culture and the entertainment media. As shortcuts for reducing complexity, these schema allow any individual—whether a lay citizen, journalist, or policymaker—to categorize new information quickly and efficiently, based on how that information is framed in the media (*5*). In sum, a one-size message about science will not fit all audiences.

We suggest that science organizations work with communication researchers, conducting focus groups, surveys, and experiments that explore how different audiences interpret topics such as climate change or evolution. On the basis of this research, messages can be tailored to fit with specific types of media outlets and to resonate with the background of their particular audience.

It is encouraging that the Letter writers agree on a few central principles. First, framing as a concept has strong roots in the social sciences. Second, framing is already central—intentional or not—to traditional science communication efforts. Third, when applied responsibly and ethically, framing can be a valuable tool for scientists in engaging nontraditional audiences.

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CORRECTIONS AND CLARIFICATIONS

News Focus: "Exploring the prehistory of Europe, in a few bold leaps" by J. Bohannon (13 July, p. 188). On page 189, the caption to a photograph of stone tools incorrectly calls them "Neolithic" in date. It should have read "pre-Neolithic."

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Deep Mixing of ^{3}He: Reconciling Big Bang and Stellar Nucleosynthesis"

Dana S. Balser, Robert T. Rood, T. M. Bania

Eggleton *et al.* (Reports, 8 December 2006, p. 1580) reported on a deep-mixing mechanism in low-mass stars caused by a Rayleigh-Taylor instability that destroys all of the helium isotope ^{3}He produced during the star's lifetime. Observations of ^{3}He in planetary nebulae, however, indicate that some stars produce prodigious amounts of ^{3}He. This is inconsistent with the claim that all low-mass stars should destroy ^{3}He.

Full text at www.sciencemag.org/cgi/content/full/317/5842/1170b

Undergraduate Education in Jordan

I WAS SURPRISED THAT THE MIDDLE EAST WAS not mentioned in the Special Section "The World of Undergraduate Education" (6 July, p. 63–81). The Middle East constitutes 2.9% of the world's population and plays a prominent role in international politics, and the education of its population is a relevant international issue. For details on undergraduate education in various Arab states in the Middle East, go to the UNESCO Web site (www.unesco.org).

In 2005, the gross enrollment ratio (*1*) for undergraduate universities in Jordan was about 39%, and females make up 49% of those enrolled (*2*). There are 22 (private and public) universities in Jordan, which is a high number since the population of Jordan is only 5.375 million.

We have many of the problems discussed in the Special Section, such as using English as the language for science as in the Austrian example ("'Can't have a career… without English,'" J. Bohannon, p. 73) and changing the curriculum from heavy memorization to a more hands-on approach, as has been done in South Korea ("'A strong voice' for course reform," R. Stone, p. 76). Also, our teaching load is very heavy, leaving little time for research.

We are pioneering problem-based learning (PBL, as mentioned in the UK article, "'Much of what we were doing didn't work,'" D. Clery, p. 68) in Jordan, and resistance is high. Older faculty are not interested. It would be nice to have an open dialogue to share experiences and tactics for introducing such methodology and addressing problems. I would suggest having a forum and in the future an international conference to discuss these issues.

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References and Notes

1. The number of students enrolled in a level of education as a percentage of the population in the relevant age group for that level.
2. See www.unesco.org.

Data-Driven Education Research

I APPROACHED THE RECENT SPECIAL SECTION on undergraduate science education ("The World of Undergraduate Education," 6 July, pp. 63–81) with great anticipation. Clearly, this is a vitally important topic for everyone—not just those interested in science education, since the connection between effective, inclusive undergraduate science education and national competitiveness is well documented (*1*). However, I was dismayed by the way *Science* chose to report on the worldwide state of science education. There is a growing body of data-driven research on "what works" to improve outcomes related to teaching, learning, and student retention [some of which has been published in *Science* (*2*)], yet this was ignored in favor of reports containing mainly opinion and hearsay. Private empiricism—where we believe something because of our own personal experience—is not appropriate for scientists, yet when it comes to education, personal experience seems to be an acceptable substitute for evidence. Unfortunately, most scientists' beliefs about education are rarely based on objective evidence, but rather on what they imagine to be true. Although personal experience in the classroom can give valuable insights, it is not data.

We now have many effective research-based ways to improve the outcomes for undergraduate science education and to assess student learning and achievement (*3*). There is a great deal of research on what works, so why is higher education in the sciences so resistant to change? Why does the faculty in your roundtable discussion not know about this research? Why do people who would never accept scientific information without data and theoretic underpinnings, embrace conventional wisdom and personal beliefs when it comes to education?

Could it be the perceived relative unimportance of education efficacy, compared with traditional research productivity? Or is it that faculty are simply unaware of the advances that have been made in science education? Even in departments where the primary focus is undergraduate education, often little attention is paid to research on teaching and learning. Whatever the reason, it is simply unacceptable that the flagship journal of AAAS reports opinion as fact and personal belief systems as evidence.

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3. Much of this work has been funded by the National Science Foundation under a number of programs, yet I see no mention of any of this work in any of the articles.

Editor's Note: Science publishes a monthly feature, the Education Forum, which focuses on data-driven education research.

EVOLUTIONARY BIOLOGY

Postgenomic Musings

Massimo Pigliucci

Everyone in biology keeps predicting that the next few years will bring answers to some of the major open questions in evolutionary biology, but there seems to be disagreement on what, exactly, those questions are. Enthusiasts of the various "-omics" (genomics, proteomics, transcriptomics, metabolomics, and even phenomics) believe, as Michael Lynch puts it in the final chapter of *The Origins of Genome Architecture*, that "we can be confident of two things: the basic theoretical machinery for understanding the evolutionary process is well established, and we will soon be effectively unlimited by the availability of information at the DNA level." Others (*1*–*4*), among whom Lynch for some reason singles out Sean Carroll (*5*) for special criticism, are a bit more skeptical. They maintain that we are still missing some explanatory principles accounting for the complexity of living organisms and that the tsunami of "-omics" information, although valuable, is actually hitting a field that is unprepared for it, both conceptually and in terms of analytical tools.

The Origins of Genome Architecture

by Michael Lynch

Sinauer Associates, Sunderland, MA, 2007. 510 pp. $59.95. ISBN 9780878934843.

But before we get to the controversy, let me say that the book's first 12 chapters are a must-read for anyone interested in the evolution of genomes. This *Origins* represents a serious, valiant, and highly scholarly attempt at making sense of the new data provided by the genomic revolution. To that aim, Lynch deploys the full array of conceptual tools that make up the modern synthesis paradigm in evolutionary biology.

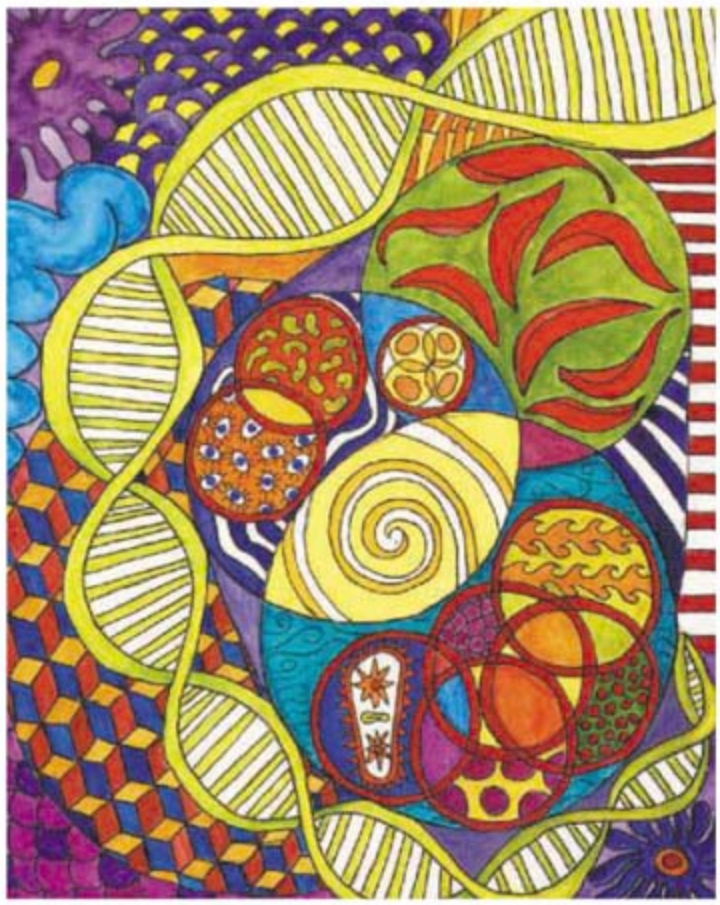
Lynch (an evolutionary biologist at Indiana University) guides us through a host of fascinating phenomena, from the evolution of sex chromosomes to the disappearance of operons in eukaryotes, from the population biology of transposons to the mechanisms of origin and loss of introns. Throughout, he reminds evolutionary biologists (and perhaps lets some molecular biologists know for the first time) that the "population thinking" so central to the modern synthesis, and in particular the solidly developed theory of population genetics, ought to be part of any postgenomic understanding of molecular evolution.

One of the central theses of the book is that natural selection is not necessarily the central evolutionary mechanism, as quite a bit of the details of genomic structures and evolution can be accounted for by invoking the neutral mechanisms of mutation, recombination, and drift. Lynch is certainly correct on this point, and he backs his argument with much empirical and theoretical detail. Yet, we must be hanging around with different crowds, because I hardly know anybody who would seriously contend that evolution is just a matter of natural selection. Lynch himself cites the now-classic paper by Gould and Lewontin (*6*) railing against "panselectionism," and most evolutionary biologists have already gotten the message.

But the really interesting, and certainly debatable, part of the book is its last chapter, "Genomfart" (from Swedish for "the way forward," we are told). There Lynch honestly states at the onset that he is going to shift gear and engage in an advocacy piece, something that I found refreshing: scientists have opinions, and they are most interesting when they are controversial. I have little patience for the pretense of a "fair and balanced view," when we all know that balance comes out of discussions and disagreements among peers, not from the point of view of a single individual (*7*). Lynch's thesis, as mentioned above, is that the theoretical apparatus of evolutionary theory is complete and that people should stop whining about missing pieces and the need for a new synthesis: just study your population genetics and everything will be all right.

This is, of course, a perfectly respectable opinion—although the repeated, if oblique, parallels Lynch draws between legitimate scientific opponents of his view and creationists who advocate intelligent design become increasingly irritating by the end of the chapter. Lynch, however, seems convinced that all that evolutionary theory has to explain is changes in allelic frequencies within populations. If that were indeed the case, the job is done, and we are now left with simply systematizing the huge amounts of information coming forth from genomic studies. As Carroll complains [in (*8*), quoted by Lynch], this is a rather uninspiring theme.

Lynch's comment that science isn't about inspiration (I guess it truly must be about perspiration), however, misses Carroll's point: what the modern synthesis has not given us is a theory of form, and applying population genetics to genomics—as valuable an exercise as that is in its own right—isn't going to give us one either. As much as genes are fundamental to the evolutionary process, there is much more to biology than genes and their dynamics. The very fact that molecular biologists are now talking (albeit often naïvely) about higher-level "-omics," all the way to phenomics, means that they appreciate that genomes are only a part of the story, arguably the simplest part to figure out.



CREDIT: LEWIS RIFKOWITZ, GUAM/COURTESY SINAUER ASSOCIATES

Lynch correctly identifies complexity, modularity, robustness, and evolvability as some of the key concepts of the recently emerged field of evo-devo (evolution of development), but he dismisses them as "buzzwords," glossing over mounting empirical and theoretical efforts aimed at articulating these notions and exploring their relations with the standard modern synthesis. Lynch makes a big deal out of the claim that the burden of proof is on people who think these and other ideas will be useful during the shaping

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of an extended synthesis in evolutionary biology. Fair enough, although one has only to read some of the several books in this field that have come out during the last decade to see that people aren't simply shooting the breeze.

But the burden-of-proof argument cuts both ways. Lynch boldly claims that "many (and probably most) aspects of genomic biology that superficially appear to have adaptive roots … are almost certainly also products of nonadaptive processes," but all we get in support of this position is a plausibility argument. Even though I agree with his contention that neutral processes have contributed to the evolution of genomes (but not, I am willing to bet, of phenomes) to a much higher degree than usually acknowledged, the evidence Lynch adduces is far from overwhelming. Throughout the book, we are treated to a series of plausible scenarios about the evolution of introns, transposons, spliceosomes, and the like. These scenarios are backed by clever applications of population genetics theory (most of which has been developed for simple one- or two-loci systems, not for genomics), but they hardly meet the high standard of historical proof (if there can be any such thing).

Lynch claims that nonadaptive processes should be considered as null hypotheses, but this gives him the unfair advantage of shifting the burden of proof against selective scenarios. What justifies this move is not at all clear, because Lynch thinks of selection as only one of the four fundamental mechanisms of evolution: if it is one of four, why treat it as a special category? To see how easily the table can be turned, just consider Dennett's diametrically opposite position that natural selection should be treated as the default explanation for complex phenotypes, unless one can show that it didn't play a role (*9*). A truly fair and balanced approach is to simply treat any hypothesis as an equal contender in the set of plausible explanations, and see how it fares against its opponents without the advantage of playing on a home field.

Ultimately, the main reason we need an expansion of the modern synthesis was pointed out by Popper several years ago: "[the Darwinian theory] is strictly a theory of genes, yet the phenomenon that has to be explained is that of the transmutation of form" (*10*). Lynch's contribution in *The Origins of Genome Architecture* goes a long way toward completing our explanation of how genes (and genomes) change over time. Nonetheless, although indeed necessary, population genetics is not even close to sufficient for understanding how phenotypes evolve. There is much more to do, and a large undiscovered country lies out there. Let's take a look.

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HISTORY OF SCIENCE

The U.S. in the Rebuilding of European Science

Jean-Paul Gaudillière

One day in 1946, the French biochemist Jacques Monod visited the laboratories at the marine biological station in Woods Hole. The visit made a strong impression on him, as he noted in a letter to his wife:

> Very big laboratories, huge library, three seminars a week, impressive organization, etc. The idea that 350 biologists are working here, that they accumulate observations; that they complete experiments, measurements, weightings; that they operate Warburg apparatus, centrifuges, and microtomes while piling up articles. All this has a somehow depressing effect on me. I am used to thinking that my work is something rare, highly personal, something I have almost invented. In my understanding, this is what makes it valuable. Here it is no longer possible to cherish such illusions. I feel the same way I felt on [Jones] Beach, when facing 50,000 cars and 500,000 bathers.

This reaction was not rare. European scientists traveling in the United States during the first decade after World War II experienced mixed feelings. They perceived the U.S. research system simultaneously as a model, a challenge, and a threat.

Such ambiguous relationships are at the center of John Krige's *American Hegemony and the Postwar Reconstruction of Science in Europe*. The issue of the role the sciences played in transatlantic affairs after 1945 is important. We all suspect that U.S. aid was as crucial to the reconstruction of European science as it was to the economic reconstruction of the old continent. However, this conclusion is unsubstantiated, because historians of science have rarely addressed the question. When discussing science and the Cold War, they have explored the intellectual achievements of the period, the advent of big science as a system of funding, or the material culture of the physics laboratory. Krige's novel and timely perspective has been to investigate the mobilization of science for general political goals and more precisely to explore the uses of science policy as an instrument in the construction of U.S. postwar hegemony.

American Hegemony and the Postwar Reconstruction of Science in Europe

by John Krige

MIT Press, Cambridge, MA, 2006. 388 pp. $40, £25.95. ISBN 9780262112970. Transformations: Studies in the History of Science and Technology.

Hegemony is evidently a question of power, but it does not simply mean order, control, and command. U.S. elites of the postwar era placed a strong emphasis on the intimate and quasi-natural alliance of market economy, freedom, and democracy as the essence of American specificity. As a consequence, Krige (a historian at the Georgia Institute of Technology) suggests, hegemony was not only to be manifested and reproduced but also to be accepted by those who had to live with it—and to some extent co-constructed with them, at least with those living on the old continent. The scientific relations between the United States and (Western) European countries constitute a privileged terrain for evaluating this thesis because the engagement of the United States, both governmental and private, was massive and, the book demonstrates, had a substantial impact on the reshaping of European science.

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The seven core chapters present case studies based on a remarkable set of U.S. archives. They provide immensely valuable and original information, especially when dealing with developments that other historians have previously analyzed from a European and more intellectual perspective (for example, the growth of nuclear physics and the rise of molecular biology).

The book contrasts two periods. The earlier one was shaped by the Marshall Plan, which first put science on the agenda of postwar international affairs. The case of Germany is typical. The initial policy was to "cripple down" German industrial and military capabilities. That resulted in a tight control of all research activities under the occupation forces. Impossible to sustain in the context of a mounting Cold War, it was replaced in 1948 with the idea that the local scientists should contribute to the defense of the "Free World." U.S. authorities adopted a policy of selective grants that barred nothing except military research, and the local Marshall aid included specific financing for the German scientific instrument industry.

This logic of heavily political aid did not only determine the initiatives of the U.S. government such as those of the Office of Naval Research, one of the first federal institutions to send researchers on European tours to evaluate needs and possibilities. Private philanthropic foundations also took up the prospects of restoration. The book's two chapters on the Rockefeller Foundation's policy in France are especially enlightening. They show how the foundation quickly resumed its prewar practices of close partnership with a core of elite scientists, whom it supported with travel and equipment grants, and also adapted to the new circumstances. Rockefeller officers thus agreed to give the French Centre National de la Recherche Scientifique (a governmental agency gathering full-time researchers in state laboratories outside the university) major grants to be administered collectively. Giving the French physicists and biologists access to the most recent instrumentation—in a continuation of prewar Rockefeller Foundation policies supporting the development of physical and chemical techniques for the study of life—was deemed an essential mean for reshaping and modernizing a system plagued with isolation, poverty, and a rigid hierarchy.

One major paradox of the period is that an emphasis on academic freedom and purity and the absence of political engagement flourished among U.S. scientists and policy-makers precisely at a time when researchers' ties to the state and the military had become stronger than ever. A peculiar equation linking good science, liberal democracy, and the market economy justified policies that would have been considered unacceptable 20 years earlier. The liberals in charge of the Rockefeller Foundation thus gradually adopted the notion that "red" or even "pink" scientists could not benefit from grants, that a researcher with communist inclinations could not (by definition) be a good and free scientist. Thus, in spite of his intimate knowledge of the United States and his prewar acquaintances there, the French biochemist Boris Ephrussi had a very difficult time defending the prospect of a major grant for the creation of a genetic institute in a country where the communist party benefited from a quarter of the votes, where the Atomic Energy Commission was under the lead of Frédéric Joliot-Curie, a party member, and where (the New York officers thought) left-minded geneticists might well support Lysenko.

The reconstruction that Krige discusses reached a turning point in the second half of the 1950s. In the context of the 1956 uprising in Hungary and the consciousness that any nuclear war would annihilate both empires, U.S. officials understood the launch of Sputnik as a portent of a coming scientific supremacy of the Soviet Union, a supremacy that was to be avoided by all means. They sought to solve the alleged western "manpower problem" in a transatlantic rather than an American way, with the North Atlantic Treaty Organization in the leading role. During the 1960s, NATO started to distribute fellowships and organize meetings on a grand scale, supporting the biological and the social as well as the physical sciences. The book vividly describes how NATO collaborated with the Ford Foundation in turning CERN into a truly collective platform visited by dozens of U.S. high-energy physicists engaged in an ongoing and highly competitive dialog with their European colleagues.

All projects were not so successful. Krige's fine-grained analysis of the 1960s plan to create a "European MIT" shows how misconceived were some plans aiming at a simple transposition of U.S. practices. The MIT model was defined as an international teaching institution: autonomous from the local universities, promoting interdisciplinary research, combining the acquisition of knowledge and the development of technologies, and strongly linked to industry. This NATO-backed European MIT did not die because de Gaulle opposed its creation, although the deterioration of relations between France and NATO during the 1960s did play a role. Rather, it failed because the project met strong resistance in universities in France, Germany, and the United Kingdom because it would drain some of the best brains out of the national research systems precisely at a time when these institutions were experiencing major reorganization and rapid growth.

Krige's account provides strong support for his concept of a co-produced hegemony. He convincingly combines the idea of an American empire engaged in the defense of free-market economy, individual rights, and political democracy with the perception of a science radically changed by the Cold War. The hegemony the United States exerted was consensual in the sense that important segments of the scientific elite in Europe shared the values associated with the permanent mobilization of research and therefore willingly participated in the design and implementation of "Atlantic" policies. American hegemony nonetheless meant uneven power and uneven access to resources, with the unavoidable failures that originate in one-sided views.

Is this co-produced hegemony purely a thing of the past? One must recognize that the nature and ways of operating of the "empire" have been dramatically altered in the 1980s and 1990s through an increasing emphasis on global markets, technological innovation, and corporate research and development. Nonetheless, the example of the failed European MIT offers a good reminder that history matters when looking at contemporary science policies.

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RETENTION

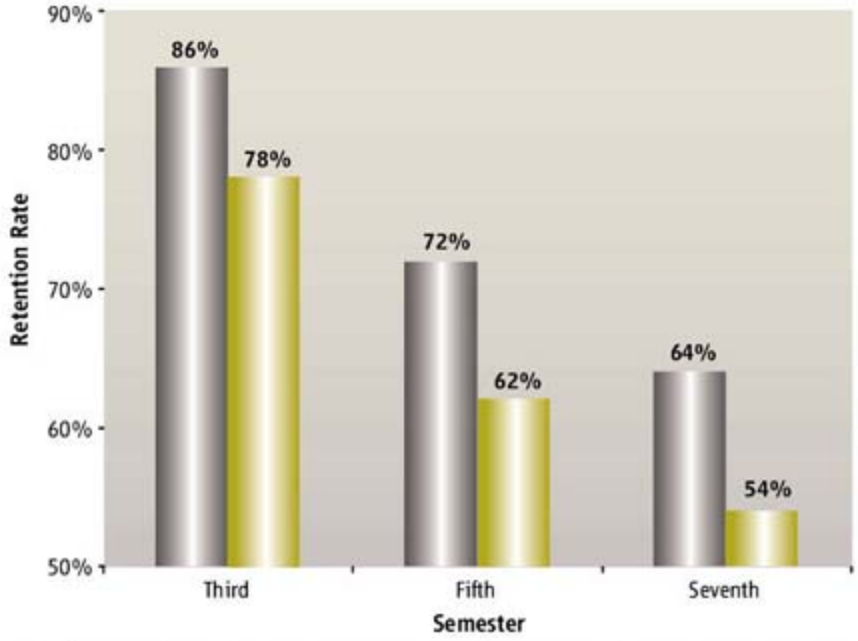
Engineering Education Research Aids Instruction

Fewer students leave engineering studies when education programs link concepts to real-world practice.

Norman L. Fortenberry,[1]* Jacquelyn F. Sullivan,[2]* Peter N. Jordan,[3] Daniel W. Knight[2]

Discipline-based education research seeks to marry deep knowledge of the discipline with similarly deep knowledge of learning and pedagogy (*1*, *2*) and may encourage college and university faculty members to bring more rigor to classroom instruction. For example, the physics-based education research community has used tools such as the Force Concept Inventory (*3*) to determine that students taught with interactive teaching techniques developed from discipline-based education research [such as Peer Instruction (*4*, *5*)] better understand the concepts of Newtonian physics than do students taught in a lecture-based format. Within the engineering community, the ultimate aims of such research include the creation of education programs that attract more, and more diverse, students to the study of engineering; retain more of the students who are enrolled; deepen students' understanding of engineering concepts; broaden students' appreciation of engineering's role in meeting the needs of a global society; and better prepare students for further study or professional practice. In pursuing these aims, research in engineering education looks beyond questions solely devoted to teaching, learning, and assessment; it also examines issues associated with faculty rewards (*6*) and the organizational dynamics of engineering departments (*7*, *8*).

Although not all engineering faculty will engage in such research, we contend that all should learn and benefit from its findings. Our commitment to engineering-based education research does not devalue the work of researchers in colleges of education or that of cognitive or social scientists. Rather, we emphasize the maturation of the engineering education research community and the increased value attached to the emerging field by the academic engineering community.



Gains in retention. The FYEP course improved retention of engineering students into the third, fifth, and seventh semester. There were 2128 students who took the FYEP course (gray) and 2942 students who did not (gold). All retention gains over expected retention rates shown are significant ($P < 0.05$).

Past, Present, and Future

In the 1990s, centers for research on engineering education opened on several campuses, with foci ranging from foundational research to innovative approaches to curriculum, learning, teaching, and assessment. In 2001, the National Science Foundation initiated support for Centers for Learning and Teaching focused on engineering and technology education (*9*, *10*). In 2002, the National Academy of Engineering shifted from solely providing advice to actively enhancing engineering education by fostering the growth of a community of engineers conducting education research and translating research results into more effective and efficient educational practices (*11*).

More recently, departments of engineering education were opened at Purdue (2004), Virginia Polytechnic Institute and State University (2004), and Utah State (2005) and announced at Clemson (2007). The emergence of these departments marks the transition from isolated individual researchers to academic communities devoted to the scholarship of engineering education.

The *Journal of Engineering Education* was repositioned in January 2003 to focus on publishing scholarly research in engineering education. The change was celebrated with a special issue (*12*), and the journal continues to focus on advancing the rigor and recognition of engineering education research (*13*).

The 2005 and 2006 Engineering Education Research Colloquies (EERC) identified five research areas that will serve as the foundation for the new discipline of engineering education (*14*): (i) engineering epistemologies—research on what constitutes engineering thinking and knowledge in social contexts now and into the future; (ii) engineering learning mechanisms—research on engineering learners' developing knowledge and competencies in context; (iii) engineering learning systems—research on instructional culture, institutional infrastructure, and epistemology of engineering educators; (iv) engineering diversity and inclusiveness—research on how diverse human talents contribute more robust solutions to global challenges and reinforce the relevance of the profession to all sectors of society; and (v) engineering assessment—research on, and the development of, assessment methods, instruments, and metrics to inform engineering education practice and learning.

Low rates of student retention within the discipline have heightened concerns in the engineering community about the structure, content, and delivery of engineering education. Although many engineering programs allow only a stringently prescreened population to enroll, on average, only 56% of undergraduate students admitted nationally

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into engineering disciplines are retained to graduation, with some schools reporting retention rates of only 30%. Academic difficulty is not why these students change course (*15*), leading the engineering education community to view these loss rates as indicators of defects within the system of engineering education that should be corrected. One application of engineering education research, developed with the goal of increasing retention rates, is the First-Year Engineering Projects (FYEP) course at the University of Colorado at Boulder.

The FYEP Course

The FYEP course was designed in the mid-1990s in response to research on other project-based engineering courses. Key principles included collaborative and team-based learning, experiential projects, open-ended design, and supportive instruction (*16*).

The FYEP course connects the conceptual and educational side of engineering with professional practice. This is primarily accomplished through a 13-week project that introduces first-year students to the design-build-test cycle of product prototype development (wherein a new object to meet a stated or perceived customer need is conceived, designed, realized as a physical object, and tested to verify that it meets requirements) in a team-based setting, supported by experimental testing (*17*). The innovations at the University of Colorado at Boulder are consistent with the results of previous science and engineering education research on experiential, interactive, and collaborative learning (*18–24*)

Only some of the 11 engineering programs at the University of Colorado at Boulder require the FYEP; for all others it is an accepted technical elective. This results in, on average, half of the incoming first-year student cohorts taking the class, which provides a useful comparative data set; it's large, longitudinal, and multidisciplinary, and it contains a reasonable control group. No significant difference in retention was found between the required and volunteer FYEP takers, implying no volunteer effect.

To examine the impact of the course on student attrition, we gathered retention data across eight cohorts from the Fall 1994 through Fall 2002 semesters. This data set contained 5070 first-year engineering students, consisting of 2128 students (42%) who took the FYEP course and 2942 students (58%) who did not take the course. The sample included 1015 women and 4055 men, and included 3992 Caucasian, 402 Asian-American, 290 Latino, 80 African-American, and 41 Native-American students. Student ethnicity data, provided by the university, reflected the self-reported ethnicity on a student's admission application. An additional 265 students were classified as "unknown ethnicity" and were not included in the ethnicity analysis. The study sample incorporated only students who took the FYEP course as first-year engineering students; transfer students were excluded, as were students who were not engineering majors or who took the course after their first year. Engineering program retention was assessed at the third, fifth, and seventh semester for all students in the sample. Logistic regression and chi-square statistical tests were used to test for differences in retention between students who did and those who did not take the FYEP course and to test for differential impacts by both gender and ethnicity (*25*).

Retention Results

Across students, those who took the FYEP course were retained at a higher level through the seventh semester ($P < 0.05$) (see graph on page 1175) (25). Logistic regression analysis indicated no statistically significant indications that a first-year design project course has a differential impact by gender or ethnicity. Because the course was taught by multiple instructors during the 8-year period under study, no instructor effect was inferred.

A pattern of elevated retention for women at the seventh semester suggests that additional focus on course elements and pedagogy could be fruitful. The analysis by ethnicity was likely influenced by low sample sizes for Latino, African-American, and Native-American students. However, regardless of gender or ethnicity, retention in engineering is higher among students who take the FYEP course.

These results add to the growing body of evidence demonstrating that first-year projects-based curricula promote retention of engineering students (*26*).

Conclusion

Although a 64% retention rate is still too low for students that are heavily screened before admission to the major, it represents an improvement on the national engineering retention rate of 56%. Given that Seymour and Hewitt (*15*) have reported retention rates of 42% in the biological sciences, 29.9% in the physical sciences, and 29.2% in mathematics, why should we seek still higher engineering retention rates? Moller-Wong and Eide (*27*) organized attrition factors into student's background, college administrative issues, academic and social integration, attitude and motivation, and fit within an institution; we suggest that all except a student's background are subject to institutional intervention and improvement. Conceding that some students will decide that engineering is not right for them, we believe that the overwhelming majority of engineering students should graduate in engineering, and retention rates above 80% should be our aspiration. Engineering retention improvement over the past decade (*15*) suggests that great strides are possible; our challenge is to make the possible probable.

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GEOPHYSICS

Mapping the Earth's Engine

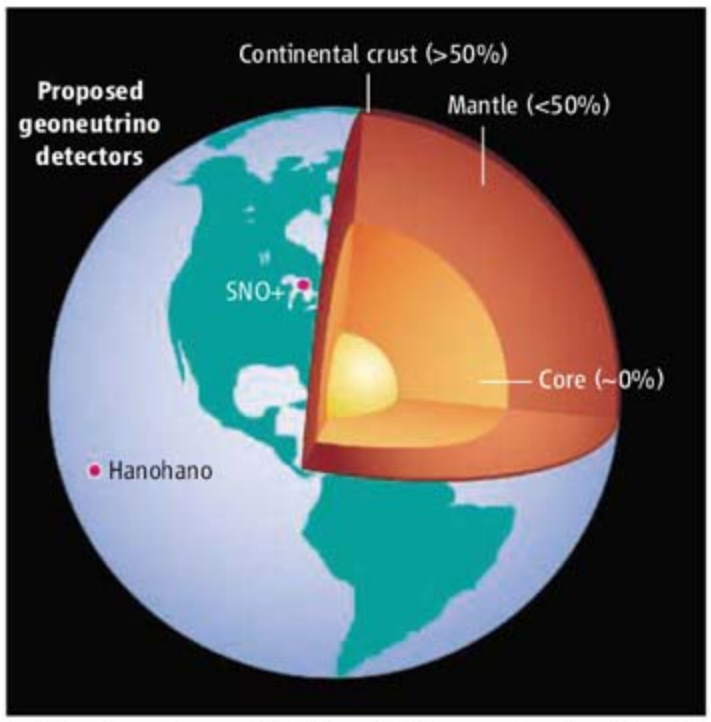
Neutrinos created by nuclear decay may allow geoscientists to measure the distribution of radioactive elements in the Earth.

William F. McDonough

Particle physicists and geophysicists rarely meet to compare notes, but earlier this year researchers from these two disciplines gathered to discuss antineutrinos (the antiparticle of the neutrino) (*1*). These fundamental particles are a by-product of reactions occurring in nuclear reactors and pass easily through Earth, but they are also generated deep inside Earth by the natural radioactive decay of uranium, thorium, and potassium (in which case they are called geoneutrinos). Particle physicists have recently shown that it is possible to detect geoneutrinos and thus establish limits on the amount of radioactive energy produced in the interior of our planet (*2*). This year's joint meeting was aimed at enhancing communication between the two disciplines in order to better constrain the distribution of Earth's radioactive elements.

Researchers from the Kamioka Liquid scintillator Anti-Neutrino Detector (KamLAND) in Japan reported results that are consistent with the power output produced from the decay of thorium and uranium (16 TW), and the abundances of these elements in Earth, as estimated by geoscientists (*3*). (Potassium geoneutrinos cannot be detected at present due to the high background in this region of the spectrum.) The initial measurement is also broadly consistent with the Th/U ratio for Earth being equal to that of chondritic meteorites, which is a fundamental assumption used by geochemists to model planetary compositions. However, the upper power limit determined by the experiment (60 TW at the 3σ limit) exceeds Earth's surface heat flow by a factor of 1.5 and is thus not very useful as a constraint for the models.

Nevertheless, there is great excitement within the two communities, as advances in antineutrino detection are anticipated. The KamLAND detector was intentionally sited near nuclear reactors in order to characterize antineutrino oscillation parameters (the reactor produces so-called electron antineutrinos, and antineutrinos can oscillate between the three different "flavors"—the electron, muon, and tau antineutrinos)—and sense fluctuations in reactor power output. Consequently, the reactor signal overwhelmed the geoneutrino signal. New detectors are being developed, deployed, and positioned in locations that have substantially smaller contributions from nuclear reactors, and thus will provide more precise measurements of neutrinos and antineutrinos to both the Earth science and astrophysical communities.



Inside story. One model of the distribution of radioactive elements potassium, thorium, and uranium in Earth. New antineutrino detectors in Canada (SNO+) and Hawaii (HANOHANO) should allow more precise determination of these distributions.

In addition to detecting geoneutrinos, these facilities are designed to detect neutrinos from supernovae and determine their oscillation properties (like antineutrinos, neutrinos can oscillate among their three different states). As particle physicists continue to count geoneutrinos, the signal-to-noise ratio will improve and, with more counts, the uncertainty in the radioactive energy budget of Earth will shrink and the measured Th/U ratio of the planet will be determined to a greater precision. Measurement uncertainties of 10% or better are possible with the new detectors, and are achievable with only 4 years of counting.

What does this mean for the Earth sciences? Geoneutrino detectors will be sited on continental crust of different ages, including ancient cratons, the oldest pieces of continents (see the figure). One proposal is to convert the Sudbury Neutrino Observatory (SNO) to "SNO+" (*4*). This 1000-ton detector is sited in a mine in Ontario, Canada, and represents an optimal location for measuring the distribution of heat-producing elements in the ancient core of a continent. Here, the antineutrino signal will be dominated by the crustal component at about the 80% level. This experiment will provide data on the bulk composition of the continents and place limits on competing models of the continental crust's composition. The Boron Solar Neutrino experiment (Borexino) detector, situated in central Italy (and hence somewhat removed from the regions of France with many reactors), has begun counting (*5*). This detector will accumulate a geoneutrino signal from a younger continental region and surrounding Mediterranean ocean basin, thus receiving a greater proportion of its signal from the mantle.

Particle physicists from Hawaii and their colleagues from elsewhere in the United States, Japan, and Europe are proposing a 10,000-ton, portable geoneutrino detector that is deployable on the sea floor. This detector, called Hawaii Antineutrino Observatory (HANOHANO, which is also Hawaiian for "magnificent"), would allow the measurement of the geoneutrino signal coming almost exclusively from deep within Earth, far removed from the continents and nuclear reactors (*6*). Thanks to the capability of multiple deployments, this detector would provide the exciting possibility of obtaining signals from different positions on the globe.

Ultimately, these different detectors will allow Earth scientists to test various models for the vertical and lateral distribution of thorium and uranium in Earth and will yield unparalleled constraints on the composition of the continents and the deeper Earth. Insights from geoneutrinos will also allow us to decide among competing models of Earth's interior. Decades of research on the state of mantle convection have assumed wide-ranging values of the Urey ratio, the proportion of radioactive energy output to the total energy output of the planet. Geochemists have deduced a Urey ratio of ~0.4, whereas geophysicists prefer constructing mantle convection models assuming higher Urey ratios that

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range up to 1.0 (*7*). In addition, geoneutrino data, coupled with local heat-flow data, will be used to evaluate models of bulk continental crustal composition. Competing models differ by almost a factor of 2 in their concentrations of potassium, thorium, and uranium, with some models critically dependent on heat-flow data (*8*).

Beyond determining the amount and distribution of heat-producing elements in Earth, particle physicists at the workshop described future experiments, only a decade or so away from implementation, that would allow more precise determination of Earth's structure. Dispersion of neutrino beams penetrating Earth are a function of the electron density of different layers of the planet. The Earth's core, composed of high-density metal, has a markedly higher electron density than the silicate shells of Earth. Likewise, there is a marked contrast in electron density for the inner and outer core. Measurement of neutrino dispersion in these layers would substantially improve our knowledge of the absolute radius of the core and hence the precision of global seismological models. Such beam studies could also place limits on the amount of hydrogen in the core.

The range of novel experiments underway and those just over the horizon will directly interrogate the interior of Earth in exciting and unparalleled ways (*9*); these tools will essentially provide new ways of "journeying" to the center of the Earth.

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ENGINEERING

Privacy By Design

New technologies are being developed to protect the privacy of individuals in today's information society.

George Duncan

Information privacy used to come by default, mainly because of the high costs imposed on any snooper. Yet today, technology has lowered the costs of gathering information about individuals, linking personal details, storing the information, and broadcasting the results. Inexpensive networked surveillance cameras capture our digital image across time and place. Terabyte RAID (redundant array of independent disks) drives provide cheap storage. Real-time data integration software turns fragmented personal data into composite pictures of individuals (*1*). Communication that is universal, instantaneous, unlimited in capacity, and free for all (*2*) is becoming ever more plausible.

With cost barriers lowered for data capture, storage, integration, and dissemination, our privacy is no longer implicitly protected (*3*). Instead, those charged with protecting information privacy must now give it explicit attention. This is the purpose of two thought-provoking reports released this year (*4*, *5*).

In its report, the U.S. National Research Council recommends that fair information practices be adopted by businesses in the use of personal information and that mechanisms be developed to give individuals more control over the use of their information (*4*). Perhaps the most controversial recommendations involve increased privacy regulation: the establishment of a Federal Privacy Commissioner or Privacy Commission, greater federal regulation of businesses that use personal information, and more government action to protect individual information privacy.

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The report from the U.K. Royal Academy of Engineering emphasizes that, because of human rights law, organizations maintaining systems that use personal information should be accountable for designing them to provide privacy (*5*). The report recommends less intrusive data use (such as preferring client authentication—"are they valid users?"—over identification—"who are they?"), research on how camera surveillance can ignore law-abiding activities, developing clarity about privacy expectations, formation of trusted third-party organizations as guardians of personal data, and making data collection and use transparent to the data subject. It advocates strengthening the powers of the U.K. Information Commissioner to include substantial penalties for misuse of data.

There are many important reasons to use personal information. For example, under Megan's Law, Web sites permit the public to locate and identify convicted sex offenders in the United States. Depersonalized data on patient drug use can be mined to better target marketing efforts for pharmaceuticals; this approach is used, for example, by Verispan (*6*). Web-based social networks like Jaiku or Twitter facilitate peer-to-peer exchange of personal details. Road tolls can be debited electronically from a driver's personal account while monitoring every vehicle's speed and recording safety violations.

But in the wrong hands, this personal information can be used to exploit or harm individuals; for example, released sex offenders may be subject to harassment, employers may discriminate against those with certain medical conditions, children on social networks may be targeted by those with evil intent, and car owners may be held accountable for what thieves may do with their cars.

To help balance privacy concerns and the need for personal data, a new paradigm is emerging, in which system designers conduct privacy risk assessments and incorporate privacy as a fundamental design parameter. As Alan Greenspan has remarked (*7*), "The most effective means to counter technology's erosion of privacy is technology itself." To illustrate how privacy-enhancing technologies

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might work, consider three privacy-affecting systems: surveillance cameras, wireless networks, and radio-frequency identification (RFID) tags for patients.

Video surveillance cameras have become a commonplace component of security systems in public places. High-resolution images over a wide field of view can be digitally stored indefinitely to identify and track persons. Mindful of visual privacy, researchers have developed an approach to perturb all facial features so that each face matches a number of others (*8*). However, major practical problems remain in implementing such procedures, in say a football stadium, underlining the need for further research; the existing techniques are too expensive and slow to be used in general video surveillance.

The rich connectivity of wireless networks involves a spectrum shared by a wide variety of devices, such as laptops, Bluetooth headsets, and mobile phones. Because any device can be identified, tracked over time, and profiled by anyone with sufficient technical capability, this congestion raises concerns that the usual encryption procedures cannot protect an individual's locational privacy. Greenstein has identified various research challenges in designing wireless systems that are privacy-aware (*9*). The challenges include, for example, cryptographic schemes to prevent the necessary device addresses from being identified without burdensome changes to existing protocols for media access, and ways for a device to discover and bind to resources without revealing to an eavesdropper that it is doing so.

Wrong-site surgery is estimated to occur between 1300 and 2700 times per year in the United States (*10*). With an RFID tag attached to a patient, a physician in the operating room can reduce the number of such errors by verifying the correct patient, procedure, and site. The U.K. health minister Lord Hunt recently supported recommendations for such strategies (*11*). Because privacy is affected, the U.S. National Institute of Standards has recommended stringent practices in designing an RFID system (*12*, *13*). For example, only the surgeon and others with a need to know would have access. Only as much personal data are captured as is necessary; thus, the tags would not contain personal financial information. Last year, Birmingham Heartlands Hospital, UK, began to expand the use of RFID bracelets to all patients on five wards, linking them to a digital photograph and the electronic medical records for their visit.

To ensure clarity and accountability (*14*), privacy-aware systems must implement a definition of privacy that users find meaningful, reasonable, and transparent. A privacy risk assessment must be performed to identify the potential for disclosure of personal information. Disclosures must be revealed, and measures must be in place to deal with privacy failures. Access by individuals to their personal data should be easy, and mechanisms must be in place to ensure that personal data are accurate.

To ensure effectiveness, systems must make a trade-off between privacy risk and utility, but reasonable expectations for privacy must always be met. For example, a subject need not be identified by name if just authentication of the subject's role in the system is required. Achieving "adequate" privacy will require engineering innovation, managerial commitment, informed cooperation of data subjects, and social controls (legislation, regulation, codes of conduct by professional associations, and response to reactions of the public).

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MOLECULAR BIOLOGY

miRNAs in Neurodegeneration

Sébastien S. Hébert and Bart De Strooper

Noncoding microRNAs are necessary for the survival of postmitotic cells such as neurons that die in Parkinson's and other brain diseases.

The human genome sequencing effort has taught us that it takes relatively few genes to build a human being. Complexity arises from the combination of these building blocks into genetic programs that are finely tuned in space and time during cell and tissue differentiation. A major part of this regulation is performed by microRNAs (miRNAs), small RNA molecules encoded by the genome that are not translated into proteins; rather, they control the expression of genes. Deregulation of miRNA function has been implicated in human diseases including cancer and heart disease (*1*, *2*). On page 1220 of this issue, Kim *et al.* (*3*) suggest that miRNAs are essential for maintaining dopaminergic neurons in the brain, and thus could play a role in the pathogenesis of Parkinson's disease.

Similar to classical genes, regions of the genome that encode miRNAs are transcribed in the cell nucleus. Nascent miRNA transcripts are initially processed into long (up to several kilobases in length) precursor miRNAs that are then sequentially cleaved by two enzymes, Drosha and Dicer, into small functional RNAs (~22 nucleotides). These miRNAs are subsequently incorporated into an RNA-induced silencing complex (RISC), which suppresses the translation and/or promotes the degradation of target messenger RNAs (mRNAs)—RNA molecules that encode proteins—by binding to their 3′-untranslated regions (3′-UTRs) (*4*). miRNAs are abundant in the brain and are essential for efficient brain function. In this regard, expression of a brain-specific miRNA (miR-124a) in nonneuronal cells

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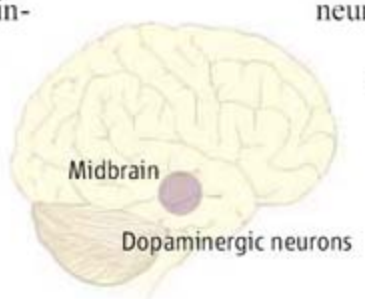
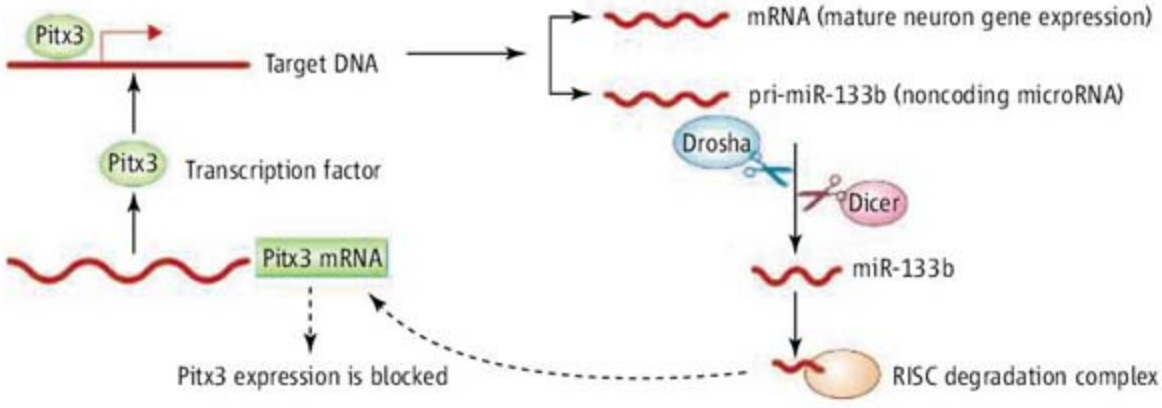
converts the overall gene-expression pattern to a neuronal one (*5*, *6*). Another brain-specific miRNA, miR-134, modulates the development of dendritic spines—neuronal protrusions that connect with other neurons—and therefore probably controls neuronal transmission and plasticity (*7*).

Recent evidence suggests that miRNAs and transcription factors work in close concert. For instance, the RE1 silencing transcription factor can inhibit transcription of miR-124a, thereby suppressing cell differentiation into neurons (*8*). Kim *et al.* observe a similar relationship between miR-133b and the transcription factor Pitx3. The pair forms a negative-feedback loop that regulates dopaminergic neuron differentiation (see the figure). Pitx3 transcribes miR-133b, which in turn suppresses Pitx3 expression.

Although Kim *et al.* provide insights into current concepts in the miRNA field and in neuronal differentiation, the implication that miRNA dysfunction could underlie certain cases of sporadic Parkinson's disease is profound given that after Alzheimer's disease, Parkinson's disease is the second most prevalent age-associated neurodegenerative disorder. The gradual loss of dopaminergic (and eventually other) neurons results in severe mobility problems and occasionally evolves into full-blown dementia. As with Alzheimer's disease, gene mutations can result in inherited forms of Parkinson's disease (*9*). Although the study of these rare familial forms has helped enormously in understanding their molecular pathogenesis, the real challenge for future research in the field is the vast number of nonfamilial cases.





Neuronal survival in the brain. An autoregulatory feedback loop composed of the transcription factor Pitx3 and miR-133b is implicated in dopaminergic neuron maturation and survival in the brain. miR-133b is deficient in the midbrain of Parkinson's disease patients and in mouse models of dopamine neuron deficiency.

The hypothesis that alterations in miRNA networks in the brain contribute to neurodegenerative disease is appealing and has been tested to a certain extent by Kim *et al.* along with previous work in mice (*3*, *10*), flies (*11*), and cultured neurons (*3*), in which the enzyme Dicer was genetically inactivated. Loss of Dicer leads to the complete absence of miRNAs and is lethal (*12*). However, Kim *et al.* show that mice lacking Dicer in specific dopamine neurons are born alive but develop a progressive loss of neurons later in life, displaying a Parkinson's disease–like phenotype. Thus, Dicer is essential for neuronal survival and loss of miRNAs may be involved in the development and/or progression of Parkinson's disease (*3*, *10*). Given that the transfer of cellular-derived small RNAs (including miRNAs) partially preserved the dopaminergic phenotype in cell culture (*3*), it is likely that the absence of miRNAs, and not the lack of other potential Dicer-related functions, is involved in the neurodegenerative process.

The next important steps are to determine the specific miRNAs responsible for neuronal cell death, the particular genetic programs and biological processes regulated by these miRNAs, and the extent to which these miRNAs play a relevant role in the neurodegenerative phenotype. The evidence presented by Kim *et al.* is somewhat ambiguous as far as relevance to neurodegeneration. Screening the expression of 224 different miRNAs obtained from brain samples of patients with Parkinson's disease and control subjects revealed notable changes in a small number of miRNAs, including miR-133b. Normally, miR-133b is enriched in the midbrain; however, it was surprisingly deficient in the brains of patients with Parkinson's disease. The relative number of patients investigated in this study is too small to draw definite conclusions about the clinical relevance of this observation. The finding that miR-133b suppresses the full differentiation of dopaminergic neurons in cell culture, whereas its expression is down-regulated in the brain of Parkinson's disease patients, is, however, puzzling. This observation suggests that miR-133b might have additional functions in dopaminergic neuronal differentiation beyond suppressing Pitx3 expression. Further work is necessary, not only to elaborate the clinical importance of these findings, but also to elucidate the full genetic program that miR-133b modulates.

Apart from the possibility that an overall loss of miRNA function could be associated with aging and could contribute to the age-related increased risk for Parkinson's and Alzheimer's disease, very specific molecular mechanisms should also be envisaged. Thus, polymorphisms in the genetic regions encoding specific miRNAs and alterations in molecular machinery (such as miRNA-processing enzymes) should be investigated. In particular, the 3′-UTR of the mRNAs encoding proteins such as α-synuclein or amyloid precursor protein should be scrutinized. Because dosage effects of these proteins are sufficient to induce Parkinson's disease (*13*) and Alzheimer's disease (*14*), respectively, further alterations that control their expression might also contribute to pathogenesis. Indeed, the neurological disorder Tourette's syndrome is associated with a variation in the binding site for a specific miRNA in the 3′-UTR of mRNAs encoding the neuronal proteins Slit and Trk-like 1 (SLITRK1) (*15*).

The work by Kim *et al.* and other recent studies (*7*, *11*) herald a new area of exciting research in the field of neurodegenerative diseases. Clinical studies will rapidly determine the extent to which miRNAs contribute to the pathogenesis of sporadic Parkinson's and Alzheimer's disease; however, the role of miRNAs as a potential therapeutic target remains a challenging question.

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STRUCTURAL BIOLOGY

Getting DNA to Unwind

Structures of proteins for DNA replication in archaea suggest common mechanisms with sliding clamp loaders and DNA helicases.

Roxana E. Georgescu and Mike O'Donnell

The initial step in duplicating a cellular genome is the unwinding of a limited region of double-stranded DNA to form a small single-stranded DNA bubble (see the figure) (*1*). In bacteria, archaea, and lower eukaryotes, the unwinding process begins at a sequence called the replication origin, which contains several conserved binding sites for a protein called the initiator. Binding of the initiator results in a nucleoprotein complex that "melts" DNA, forming the DNA bubble into which the replication machinery assembles. The architecture of the initiator-origin DNA nucleoprotein complex is largely unknown, but reports by Gaudier *et al.* on page 1213 (*2*) and by Dueber *et al.* on page 1210 (*3*) of this issue solve high-resolution structures of archaean initiator protein–origin DNA complexes that reveal several unexpected and novel features of initiator protein function.

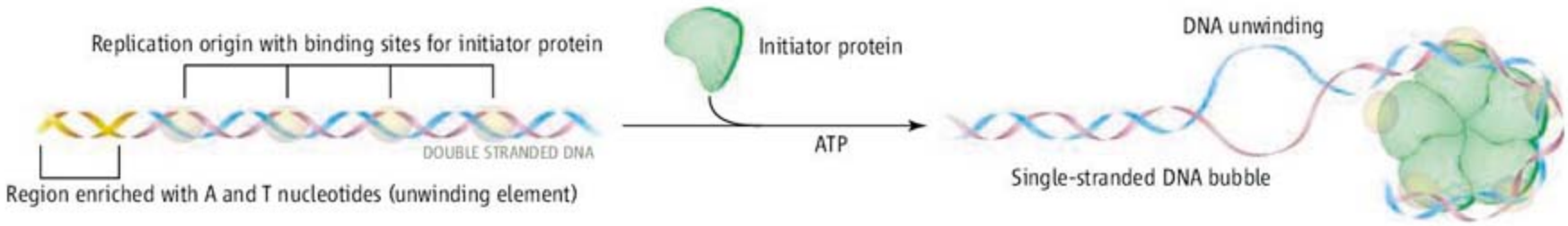
Initiator proteins in all three domains of life share homology in a region that binds adenosine triphosphate (ATP), placing them in the AAA+ family of adenosine triphosphatases (*4*). AAA+ proteins are associated with diverse cellular activities and typically function as oligomers that remodel other macromolecules. Once bound to sites within a replication origin, initiator proteins oligomerize and use ATP to separate DNA strands in a nearby region (called the duplex unwinding element) that is enriched with adenine (A) and thymine (T) nucleotides. ATP binding and hydrolysis occurs at the interface between adjacent initiator proteins, which may underlie communication and cooperative action among subunits of an AAA+ protein oligomer.

DnaA, the replication initiator in the bacterium *Escherichia coli*, is monomeric in solution and oligomerizes upon binding to multiple initiator sites at a replication origin (*5*). By contrast, the eukaryotic initiator ORC (origin recognition complex) is a tightly associated heterohexamer both in solution and when bound to DNA; five ORC subunits are thought to be AAA+ proteins (*6*–*8*). Moreover, the replication origins of higher eukaryotes lack defined initiator binding sites (*9*). But like those of bacteria, the replication origins of archaea contain several conserved initiator binding sites positioned near an A and T-rich unwinding element (*10*).

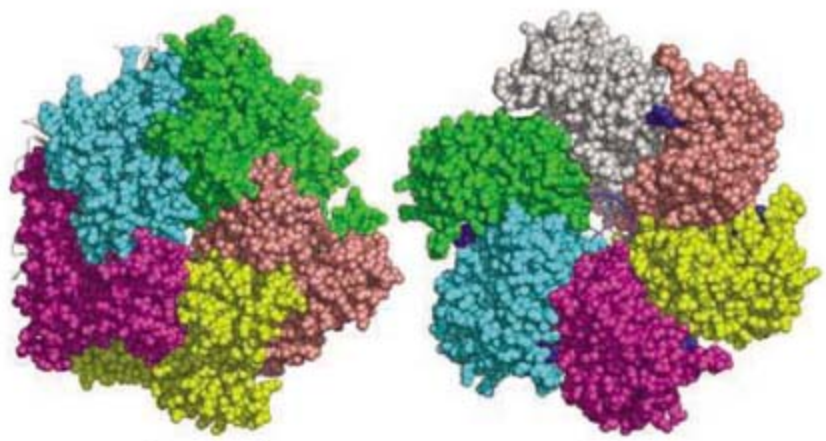
Archaea usually contain a few different but homologous AAA+ initiators known as Orc proteins. Like bacterial DnaA, archaean Orc proteins contain an AAA+ region connected to a DNA binding domain and form an oligomer upon binding the replication origin. The archaean Orc DNA binding domain has a winged helix motif. Many winged helix proteins bind as dimers to near-palindromic sites, and because archaean initiator binding sites contain a conserved symmetric dyad, it has been presumed that two Orc proteins bind to each initiator site.

Gaudier *et al.* and Dueber *et al.* present the structures of Orc-DNA complexes from two different archaea: Orc-1 bound to DNA from *Aeropyrum pernix*, and the Orc1-1–Orc1-3 heterodimer bound to two initiator sites (within one oligonucleotide) from *Sulfolobus solfataricus*. The structures reveal several unexpected features by which initiators engage DNA. Surprisingly, both studies show that only one Orc monomer binds to each initiator site. Each Orc forms a complex with adenosine diphosphate (ADP), as seen in Orc structures characterized in the absence of DNA (*11*, *12*). The winged helix motif consists of two DNA binding elements—a helix-turn-helix and a β hairpin. The two DNA binding elements of the Orc winged helix enter both the major and minor grooves of DNA, widening them, in contrast to the typical case in which only one element of the winged helix enters a groove, and the other contacts the phosphodiester backbone.

Another unexpected finding from both studies is that the AAA+ domain of Orc binds DNA directly, rather than simply mediating protein oligomerization. Interaction



Encircling and unwinding DNA. Replication origins in bacteria and archaea contain several initiator binding sites and an A and T-rich unwinding element. The *E. coli* origin is illustrated as an example. Initiator binding and hydrolysis of ATP results in oligomerization of initiator proteins and formation of a single-stranded DNA bubble, into which the DNA replication machinery will assemble.



Replication protein spirals. Structures of two AAA+ protein oligomers that bind to DNA during replication are shown: the yeast RFC clamp loader (**left**) and the papilloma virus E1 helicase (**right**).

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between the AAA+ motif and DNA imposes a unique polarity of Orc on the initiator binding site. These multiple protein-DNA contacts distort and bend DNA 20° to 35° and untwist their respective DNA sites without actually breaking hydrogen bonds between the nucleotide bases. *S. solfataricus* Orc proteins are noted for their sparse sequence-specific contacts, which is quite interesting given that higher eukaryotes lack defined replication origin sequences. Gaudier *et al.* suggest that the eukaryotic ORC may recognize specific DNA structures that can be deformed to fit into the ORC. This method of DNA recognition is used by another class of AAA+ proteins—the replication clamp loaders—which recognize DNA structure rather than sequence.

An important future goal in the study of initiator proteins is to understand the architecture of an initiator oligomer bound to a complete replication origin and how the nucleoprotein complex couples ATP hydrolysis to the unwinding of DNA. Oligomers in the other replicative AAA+ classes—clamp loaders and certain helicases—have been solved and may provide insight into the arrangement of initiator subunits within this complex. For example, both the eukaryotic RFC clamp loader (*13*) and the papillomavirus E1 helicase (*14*) form circular structures (see the second figure), and their AAA+ domains are arranged in a spiral that contacts DNA. The findings of Gaudier *et al.* and Dueber *et al.* that the AAA+ domains of archaean Orc bind directly to DNA suggest a close functional relationship of initiators to other replicative AAA+ proteins and imply that archaean initiator oligomers may also encircle DNA. Indeed, circular and helical arrangements have been observed in previous structural studies of initiator oligomers in the absence of DNA [bacterial DnaA (*15*) and eukaryotic ORC (*16*, *17*)]. The present findings bring us closer to resolving how the replication of DNA gets started and how conserved or divergent the strategies are across species.

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MATERIALS SCIENCE

Polymer Therapeutics

Polymers are finding increasing use as drugs, both in development and in clinical practice.

Kristi L. Kiick

Polymers have been used for decades as drug-delivery vehicles and implants owing to their useful mechanical properties (*1*–*3*), but were long thought too heterogeneous for use as bioactive pharmaceuticals in their own right. However, the physical properties of polymers can offer distinct advantages critical for treating human disease, including improved drug targeting and circulation, and polymer drugs have thus entered into routine clinical practice (*4*).

Various strategies have advanced the biomedical application of polymeric drugs, including the chemical attachment of drugs to a polymer scaffold, the production of polymers directly from a polymerizable drug, and the use of polymers to sequester and eliminate toxic compounds. Polymer drugs of these categories are in or near clinical application. New approaches, mainly at the research stage, exploit improved understanding and control of polymer structure in the design of polymeric drugs with biological activities controlled by polymer architecture.

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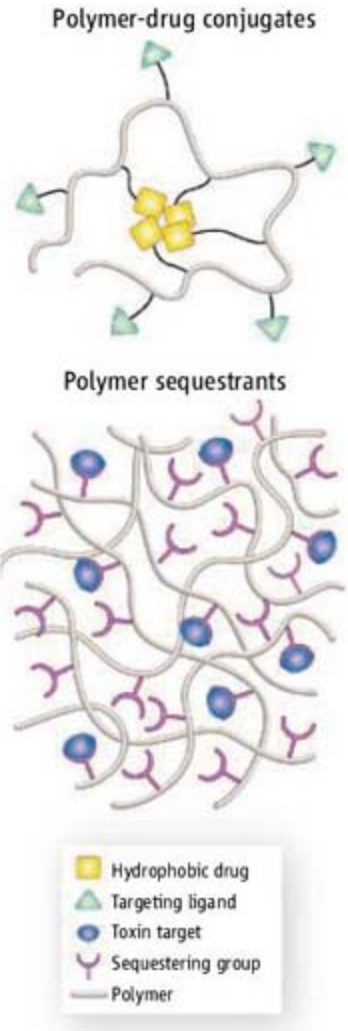
In some of the most developed and clinically applied approaches, the drug of interest is chemically attached to the polymer scaffold (see the first figure, top panel); these polymer-drug conjugates lead to improved drug targeting, circulation, and solubility. Attachment of targeting ligands to the polymer offers further enhancement in targeting, and judicious choice of the linker between the drug and polymer enables targeted liberation of drugs in response to pH, enzymatic, or redox-responsive mechanisms (*4*, *5*). In a different approach, certain drugs (such as nonsteroidal anti-inflammatory drugs and antiseptics) can be polymerized directly to yield drug-based polymeric drugs that can be easily processed and that degrade to directly release the bioactive drug (*6*).

Polymer sequestrants (see the first figure, bottom panel) have also been widely used clinically in the form of crosslinked hydrogels or resins, taking advantage of their ability to remain intact in the gastrointestinal tract and to not be absorbed through the intestinal wall. Control of their electrostatic charge and hydrophobicity has permitted their use for removal of ions, bile acids, fats, and other toxins (*7*). For example, Renagel—a crosslinked hydrogel with controlled densities of select amine groups—has been used clinically to sequester phosphate ions in patients with chronic renal failure. Additional sequestrants containing hydroxamic acid groups can arrest the intestinal absorption of dietary



Polymer-drug conjugates and polymer sequestrants.

iron and may find future use in the treatment of iron-overload conditions.

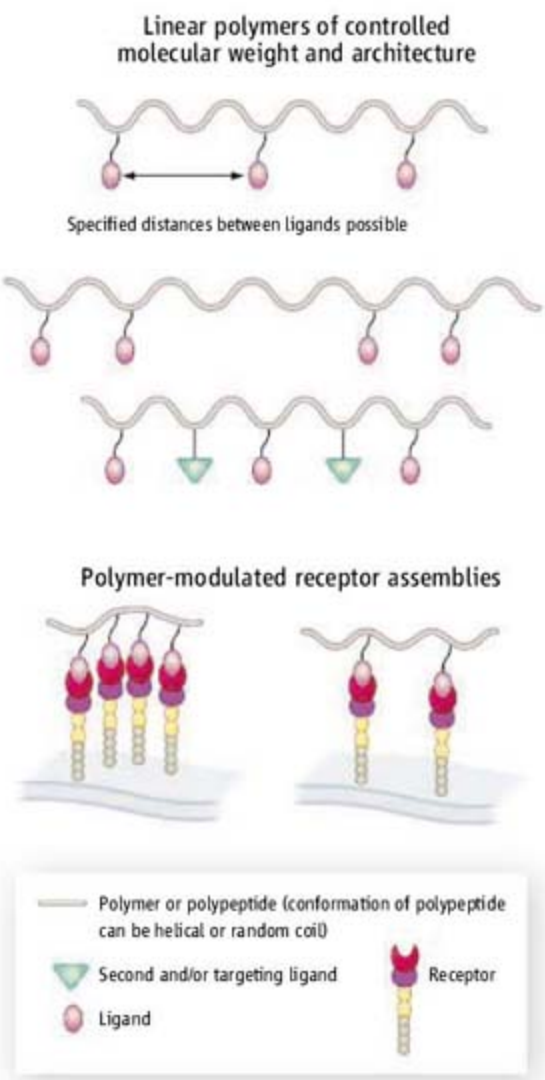
Polymeric drugs can also show therapeutic action by binding directly to biological targets. Approaches in development include co-polypeptide-based polymers that can slow the progression of multiple sclerosis by competing with autoantigens and preventing sensitization of T cells (*8*), and ligand-decorated polymers that bind efficiently to toxins (*9*).

New and exciting approaches in the design of future polymeric drugs use ligand-modified scaffolds with activities derived distinctly from controlled scaffold structure and consequent controlled presentation of ligands (see the second figure, top panel). Detailed knowledge of the biological target, informed macromolecular design, and high levels of synthetic control are all necessary to produce such polymers.

With appropriate design and synthesis, these well-defined polymers can be used to study and manipulate cell-surface–receptor assemblies (see the second figure, bottom panel). The organization of cell-surface receptors into arrays serves as a key signaling mechanism in processes such as cell adhesion, immune responses, and bacterial chemotaxis. In some cases, receptor dimerization activates maximum signaling, but often, the recruitment of a greater number of receptors to the array amplifies or otherwise alters the resulting signal. These receptor arrays occur on length scales of 1 to 100 nm. Macromolecular ligands are thus uniquely suited for manipulation of the arrays and offer enormous promise in characterizing cell surfaces, targeting specific cell types, and regulating cell activities. They may serve not only as mechanistic probes, but also as therapeutics that control cellular responses.

A variety of controlled polymerization methods have been used to produce well-defined polymers for receptor binding, with ring-opening metathesis polymerizations (ROMP) (*10*) showing much recent promise. Gestwicki and Kiessling have shown that ROMP-derived polymers of different molecular weights have different propensities for initiating chemotaxis in bacteria (*11*). Baessler *et al.* have used ROMP-derived polymers (see the second figure, top panel) to study organization of egg cell-surface receptors during fertilization. Fertilization can be inhibited by receptor dimerization by end-functionalized, ROMP-derived polymers; inhibition potency is not improved by using higher-valency or longer polymers (*12*).

Signaling functions of immune cells can also be studied and controlled with macromolecular ligands. Leukocyte surfaces contain a carbohydrate-binding protein, L-selectin, that regulates leukocyte rolling and adhesion at sites of injury, initiating the inflammatory response. Molecules that modulate L-selectin adhesion may thus be useful in regulating the inflammatory process. L-Selectin binding on the surfaces of leukocytes can be engaged via ROMP-derived multivalent ligands, and ligand potency has been shown to increase with multivalency (*13*).



Macromolecular ligands for manipulation of receptor arrays.

Multivalent ligands have also been used to manipulate B cell signaling. B cells produce antibodies in response to antigen binding. Puffer *et al.* have shown that modulating the organization of the B cell receptors alters antibody production to favor either tolerance or immunity (*14*). Binding of low-valency ligands promotes tolerance, whereas binding of high-valency ligands activates gene-expression changes necessary to stimulate antibody production. These differences are thought to result from controlled differences in receptor aggregation by the well-defined polymeric ligands, and are not observed with traditional antibody-based approaches to receptor aggregation. Such polymer approaches may therefore be useful in the treatment of autoimmune diseases and in adjuvant therapy and vaccine development.

There are many further opportunities in the development of polymers for these applications. Increasingly precise ligand placement will permit independent manipulation of ligand number and spacing, offering opportunities to tune receptor organization and cell activity. Biosynthetic methods afford unique synthetic capability in this regard, allowing production of perfectly defined polypeptide-based polymers with specific backbone conformations and with one or more different ligands in specific positions (see the second figure, top panel). Such polypeptide-based macromolecular ligands bind bacterial toxins (*15*), and offer substantial potential for manipulating cell signaling and mapping unknown receptor topologies.

Many challenges remain. Controlled trafficking of a given polymer drug, and minimization of its inflammatory and immunological properties, continue to be challenges in the design of therapeutic macromolecules. Improved molecular-level characterization of the interactions of these macromolecular drugs with their targets—for example, with advanced imaging techniques and single-molecule characterization methods—will facilitate their design. The continued development of systems biology approaches will also aid in the prediction of cellular outcomes upon drug administration. With convergence of advances in these areas, the prospects continue to be bright for the use of polymer therapeutics in the treatment of human disease.

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CLIMATE POLICY

Sir David King Urges Global Pact by 2009 to Reduce Greenhouse Gases

Wealthy and developing nations should join to approve a global pact by 2009 to sharply reduce greenhouse gas emissions and avoid "catastrophic" climate change, Sir David King, the U.K.'s chief scientific adviser, said in a lecture at AAAS on 13 July.


Sir David King at AAAS

Speaking to an overflow audience, King said that the Earth is already feeling destructive effects of human-caused climate change. But if a rigorous new agreement could be approved in 2 years and implemented by 2012, he said, atmospheric concentrations of greenhouse gases could be stabilized between 450 and 550 parts per million.

"The impacts at 450 ppm will be "dangerous," King said. But if levels were to approach 550 ppm and beyond, possible on current trends by mid-century, impacts which would become progressively more severe at higher levels include: reduced crop yields in many areas; reduced supplies of fresh water; storms, droughts, and forest fires of increasing intensity; species extinction; lethal heat waves; and coastal flooding that could create tens of millions of refugees.

"We must get global agreement," he said, "and I'm standing here in Washington [D.C.] saying: 'We need it in a very short period of time.'"

King was appointed the U.K.'s chief scientific adviser in October 2000, and serves also as director of the Surface Science Research Group at the University of Cambridge Department of Chemistry. He addressed the AAAS Annual Meeting in Seattle, Washington, in 2004, and spoke at AAAS headquarters in 2005.

Atmospheric CO_2 levels alone are now at over 380 ppm and expected to reach 400 ppm within a decade. If total greenhouse gases (GHGs) emissions peak in 2020, levels likely can be held below 550 ppm CO_2 equivalent, King said in his 13 July talk.

"We need a two-track strategy," he explained. "We must reduce emissions radically to stabilize GHGs in our atmosphere. But we also cannot avoid climate changes that are already in the system from historic emissions. We must therefore, at the same time, adapt to these impacts we cannot avoid, and we have to do so country by country."

The European Union agreed in 2007 to cut GHG emissions by 20% by 2020 compared to 1990 levels, and by 30% if part of a wider international agreement. To provide leadership, a draft Climate Change Bill, set forth on 13 March, requires the United Kingdom to reduce CO_2 emissions by 26 to 32% by 2020 and by at least 60% by 2050 over 1990 levels.

The United Kingdom's policies to reduce GHG emissions include a requirement for electricity suppliers to produce a growing percentage of power from renewable sources. In addition, measures are in place to promote energy efficiency and support development of new technologies, including the establishment of the Energy Technologies Institute, a public-private partnership of the U.K. government and industry.

Noting that fossil fuels will play a continuing role, King called carbon capture and storage "key to it all." A cap-and-trade system also will be essential to controlling emissions, he explained. In simple terms, a cap-and-trade scheme imposes strict limits on emissions from a group of industries, then grants permits for emissions; a market is created in which the permits can be sold by those who emit less and bought by those who emit more. Over time, the number of permits is reduced.

Such a system is already operating in the European Union. In the United States, eight bills pending in Congress would follow suit.

Does any such measure have a chance in the current U.S. political climate? "As I go through Washington [D.C.], I hear a willingness to listen to lessons we've learned" in the United Kingdom, said King. Later, he added: "As we move forward to early next year, I'm very much hoping to see a clear leadership position from the United States" on the climate issue.

Indeed, King expressed guarded optimism about future prospects. Leaders in oil, energy, finance, and insurance are joining the effort to mitigate global change. The emissions-reduction effort may, in time, stimulate the world economy, he said. With technological advances, improved solar power could meet all of our energy needs.

And, he said, a new global emissions pact could be on the horizon, with the United Kingdom, the United States, and other members of the G8 group of industrialized nations agreeing at their June summit on the urgent need to cut emissions. Agreements between this group and key developing nations such as China and India would be key to support the formal United Nations Framework Convention on Climate Change negotiations, he said.

"We've got a lot to play for," King concluded, "and I think we can do it."

See a video of Sir David King's lecture at www.aaas.org/go/king2007.

–Ginger Pinholster contributed to this report.

SCIENCE & SCHOOLS

Georgia Teacher Wins New AAAS Education Prize


Chris Kennedy

Chris Kennedy's class started with some colored pencils and a list—54 elements followed by bewildering strings of subscript and numbers. By the time they had finished the unique periodic table lab, the students were debating the strange electron configuration of copper in the hallway after class. The successful lesson is emblematic of the thought-provoking teaching that made Kennedy the first winner of AAAS's Leadership in Science Education Prize for High School Teachers.

The lab was an "old favorite" that Kennedy, a veteran chemistry teacher at Hiram High School in Hiram, Georgia, reworked to meet new state standards for high school science courses, which are based in part on AAAS's Project 2061's *Benchmarks for Science Literacy*.

"Many of our students are used to doing concrete activities in school, so this was a little more challenging," Kennedy said. "This is one of the first times they've had to deal with abstract concepts, since we're talking about these atoms and molecules that they can't see."

"I actually like science now that I've had his class, " said Marissa Matthews, a Hiram senior who took chemistry with Kennedy last year. "It made it easier to learn because you're actually doing stuff. You're doing it yourself."

The annual prize of $1000, supported by a AAAS donor, recognizes a high school teacher who has developed an innovative and effective classroom strategy, activity, or program that contributes to the AAAS goal of advancing science education.

Kennedy said the prize was "a bit of a shock, and humbling too, to think of the number of people out there teaching and doing absolutely wonderful things in their classrooms."

"Given the enormous challenges facing science educators today, it is especially gratifying to know that AAAS is now able to recognize the efforts of talented individuals like Mr. Kennedy with this new prize," said Jo Ellen Roseman, director of Project 2061, AAAS's science literacy initiative.

The electron configuration lab is one of Kennedy's inquiry-based lessons that encourage students to solve problems and come up with their own questions as they explore a scientific topic. Kennedy first encountered the approach as a mid-career teacher, "but there's not a lot of stuff out there for high school chemistry, not like a recipe book out there to do more inquiry in my classroom." Despite this, he forged ahead, and now spends part of each year training science teachers in inquiry-based learning.

In her letter nominating Kennedy, Paulding County Schools science coordinator Dawn Hudson praised Kennedy's work with other teachers. "He has burned copies of discs with his labs, lesson and unit plans, and other teaching tips—one per chemistry teacher in our district," she said. Many teachers in the district are trying his techniques "because they see the impact in Chris's classroom as a result," Hudson added.

One of the biggest challenges in teaching high school students "is sometimes convincing them that they can do the science, and that they're going to make it through the science. My department chair calls it the 'buy-in,' " Kennedy quipped.

Last year, Kennedy made the sale. For the first time in 12 years, none of his 95 students missed the four questions related to electron configurations on their semester exam.

For more information on the AAAS Leadership in Science Education Prize for High School Teachers, see www.aaas.org/go/scied_prize.

–Becky Ham

SCIENCE POLICY

Congress Advances Funds for Earth Observation

Four months after AAAS joined a call to preserve U.S. funding for Earth observation satellites, the U.S. House of Representatives in July restored funds to a satellite network seen as essential to weather forecasting and climate change research.

The House appropriations bill specifically increases funding for Earth-observing satellites and Earth sciences research in the FY 2008 budgets of the National Aeronautics and Space Administration (NASA) and the National Oceanic and Atmospheric Administration (NOAA). For instance, the bill includes a $60 million increase in the NASA budget for several new satellite missions recommended in a 2007 study by the National Research Council (NRC), *Earth Science and Applications from Space*.

In a statement issued in April, the AAAS Board of Directors warned that budget cuts and shifts in research priorities at NASA and NOAA could lead to "major gaps in the continuity and quality of the data gathered about the Earth from space." The board praised the NRC's report as a blueprint for restoring the satellite program.

At an 11 July hearing before the U.S. Senate Commerce, Science, and Transportation Committee, Senator Bill Nelson (D–FL) said AAAS and others had "raised concerns about the loss of climate data and climate monitoring capabilities" as the current satellite fleet ages and is replaced by less capable models. The Senate will take up an appropriations bill similar to the House measure when Congress convenes in September.

The final budget for the satellites will depend on President George W. Bush, who has threatened to veto any appropriations that surpass his own budget request. As of mid-August, Congress had already pushed its own domestic spending plan $21 billion past the president's limit, according to a new report by AAAS's R&D Budget and Policy Program.

For more R&D budget analysis, see www.aaas.org/spp/rd/.

–Becky Ham

INTERNATIONAL

Report Offers Support for Inter-American Institute

The Inter-American Institute for Global Change has produced "high-quality science" and helped build research capacity in Latin America, and its impact could be amplified if it improves communication with policy-makers, says a new review organized by AAAS.

Founded in 1992, the Inter-American Institute (IAI) focuses on the Americas and the Caribbean, a region of extraordinary biological diversity and climate variations that is beset by growing population and serious environmental problems.

The review, commissioned by the U.S. National Science Foundation, was delivered in Manaus, Brazil, in June to IAI officials representing the 19 member nations. It found that aspects of the institute's scientific work "have been internationally recognized and supported," and that IAI short-courses, workshops, and apprenticeships are vital contributions to research capacity in the Americas.

The reviewers also offered some guidance for the institute's future evolution: More research should analyze "the reciprocal links between human activities and environmental change." Stronger communication and outreach would help position IAI "as the broker of two-way dialogue between the science and decision-making communities throughout the region." And it could bolster its finances by seeking support from industry, nongovernmental groups, and other sources.

IAI Director Holm Tiessen, who joined the institute 2 years ago, said in an interview that the report offers "in a productive and in a forward-looking way some solutions to some perennial problems." Officials involved in the review praised Tiessen for moving proactively to strengthen the institute.

"There is little doubt that the IAI is as important today as it was when the governments of the Americas first created it," said Vaughan Turekian, AAAS's chief international officer. "As we look toward the future need to take further steps to promote sustainable development and well-being in the hemisphere, the IAI will take on an even more important role in informing government action."

ELECTIONS

AAAS Annual Election: Preliminary Announcement

The 2007 AAAS election of general and section officers will be held in October and November. All members will receive a ballot for election of the president-elect, members of the Board of Directors, and members of the Committee on Nominations. Members registered in one to three sections will receive ballots for election of the chair-elect, member-at-large of the Section Committee, and members of the Electorate Nominating Committee for each section.

Members enrolled in the following sections will also elect Council delegates: Atmospheric and Hydrospheric Sciences; Dentistry and Oral Health Sciences; Education; General Interest in Science and Engineering; Information, Computing, and Communication; Linguistics and Language Science; Pharmaceutical Sciences; Societal Impacts of Science and Engineering; and Statistics.

Candidates for all offices are listed below. Additional names may be placed in nomination for any office by petition submitted to the Chief Executive Officer no later than October 8. Petitions nominating candidates for president-elect, members of the Board, or members of the Committee on Nominations must bear the signatures of at least 100 members of the Association. Petitions nominating candidates for any section office must bear the signatures of at least 50 members of the section. A petition to place an additional name in nomination for any office must be accompanied by the nominee's curriculum vitae and statement of acceptance of nomination.

Biographical information for the following candidates will be enclosed with the ballots mailed to members in October.

Slate of Candidates

GENERAL ELECTION

President-Elect: Peter C. Agre, Duke Univ. School of Medicine; Peter J. Stang, Univ. of Utah

Board of Directors: Nancy Knowlton, Smithsonian Inst., National Museum of Natural History; W. Carl Lineberger, Univ. of Colorado/ JILA; Thomas A. Woolsey, Washington Univ. School of Medicine; Wm. A. Wulf, Univ. of Virginia

Committee on Nominations: Richard C. Atkinson, Univ. of California, San Diego; Jerome I. Friedman, Massachusetts Inst. of Technology; Diana Hicks, Georgia Inst. of Technology; Karen A. Holbrook, President Emerita, Ohio State Univ.; Barry J. Huebert, Univ. of Hawaii; Peter H. Raven, Missouri Botanical Garden; Lydia Villa-Komaroff, Cytonome, Inc.; Robert H. Waterston, Univ. of Washington

SECTION ELECTIONS

Agriculture, Food, and Renewable Resources

Chair Elect: Daniel R. Bush, Colorado State Univ.; Neal Van Alfen, Univ. California, Davis

Member-at-Large of the Section Committee: Sally Mackenzie, Univ. of Nebraska-Lincoln; Deon D. Stuthman, Univ. of Minnesota

Electorate Nominating Committee: Pamela J. Green, Univ. of Delaware; Nancy P. Keller, Univ. of Wisconsin-Madison; Thomas Jack Morris, Univ. of Nebraska, Lincoln; Charles W. Rice, Kansas State Univ.

Anthropology

Chair Elect: Michael A. Little, Binghamton Univ.; Margaret J. Schoeninger, Univ. of California-San Diego

Member-at-Large of the Section Committee: Clifford J. Jolly, New York Univ.; Dennis H. O'Rourke, Univ. of Utah

Electorate Nominating Committee: Terry Harrison, New York Univ.; William R. Leonard, Northwestern Univ.; Karen R. Rosenberg, Univ. of Delaware; Lisa Sattenspiel, Univ. of Missouri-Columbia

Astronomy

Chair Elect: Steven V. W. Beckwith, Johns Hopkins Univ./Space Telescope Science Institute; Mario Livio, Space Telescope Science Institute

Member-at-Large of the Section Committee: Lori E. Allen, Smithsonian Astrophysical Observatory; Nancy D. Morrison, Univ. of Toledo

Electorate Nominating Committee: Lynn R. Cominsky, Sonoma State Univ.; Margaret Meixner, Space Telescope Science Institute; Tammy Smecker-Hane, Univ. of California, Irvine; William S. Smith Jr., Association of Universities for Research in Astronomy

Atmospheric and Hydrospheric Sciences

Chair Elect: Kenneth H. Brink, Woods Hole Oceanographic Inst.; Margaret Leinen, Climos, Inc.

Member-at-Large of the Section Committee: Heidi Cullen, The Weather Channel; Eugenia Kalnay, Univ. of Maryland

Electorate Nominating Committee: David M. Glover, Woods Hole Oceanographic Inst.; Jean Lynch-Stieglitz, Georgia Inst. of Technology; Syukuro Manabe, Princeton Univ.; Terry Whitledge, Univ. of Alaska

Council Delegate: Wanda R. Ferrell, U.S. Department of Energy, Atmospheric Radiation Measurement Climate Research Facility; Claire L. Parkinson, NASA Goddard Space Flight Center

Biological Sciences

Chair Elect: Barbara L. Illman, Institute for Microbial and Biochemical Technology, U.S. Forest Service; James A. Spudich, Stanford Univ.

Member-at-Large of the Section Committee: Marnie E. Halpern, Carnegie Institution of Washington; Diana G. Myles, Univ. of California, Davis

Electorate Nominating Committee: Charles A. Ettensohn, Carnegie Mellon Univ.; David R. McClay, Duke Univ.; Michael W. Nachman, Univ. of Arizona; Baldomero "Toto" Olivera, Univ. of Utah

Chemistry

Chair Elect: Madeleine Jacobs, American Chemical Society; Geraldine Richmond, Univ. of Oregon

Member-at-Large of the Section Committee: Peter B. Armentrout, Univ. of Utah; Carol A. Fierke, Univ. of Michigan

Electorate Nominating Committee: Alison Butler, Univ. of California, Santa Barbara; David Eisenberg, Univ. of California, Los Angeles; Mark A. Ratner, Northwestern Univ.; Edward I. Solomon, Stanford Univ.

Dentistry and Oral Health Sciences

Chair Elect: David S. Carlson, Texas A&M Health Science Center; Huw F. Thomas, Univ. of Alabama at Birmingham

Member-at-Large of the Section Committee: Susan W. Herring, Univ. of Washington; Dennis F. Mangan, Univ. of Southern California

Electorate Nominating Committee: Mark W. Lingen, Univ. of Chicago; Frank C. Nichols, Univ. of Connecticut; Janet Moradian-Oldak, Univ. of Southern California; Hans-Peter Weber, Harvard School of Dental Medicine

Council Delegate: Jacques E. Nör, Univ. of Michigan; Susan Reisine, Univ. of Connecticut

Education

Chair Elect: Judith A. Dilts, James Madison Univ.; Eric J. Jolly, Science Museum of Minnesota

Member-at-Large of the Section Committee: Elizabeth S. Boylan, Barnard Coll.; Robert Tinker, The Concord Consortium

Electorate Nominating Committee: Judy Diamond, Univ. of Nebraska-Lincoln; Adam P. Fagen, Board on Life Sciences, National Research Council; Kenji Hakuta, Stanford Univ.; Susan H. Hixson, National Science Foundation

Council Delegate: Rodger W. Bybee, Biological Sciences Curriculum Study; Alan J. Friedman, consultant, New York, NY

Engineering

Chair Elect: Kenneth F. Galloway, Vanderbilt Univ.; Robert M. Nerem, Georgia Inst. of Technology

Member-at-Large of the Section Committee: Cristina H. Amon, Univ. of Toronto; Kenneth R. Diller, Univ. of Texas

Electorate Nominating Committee: Kristi S. Anseth, Univ. of Colorado; Cindy Atman, Univ. of Washington; Chris T. Hendrickson, Carnegie Mellon Univ.; John W. Rudnicki, Northwestern Univ.

General Interest in Science and Engineering

Chair Elect: Jonathan Coopersmith, Texas A&M Univ.; Charles N. Haas, Drexel Univ.; Susanna Hornig Priest, Univ. of Nevada, Las Vegas

Member-at-Large of the Section Committee: Larry Bell, Museum of Science, Boston; Erika C. Shugart, Marian Koshland Science Museum of the National Academy of Sciences

Electorate Nominating Committee: Jarvis L. Moyers, National Science Foundation; Joann Ellison Rodgers, Johns Hopkins Medicine; John L. Safko, Sr., Univ. of South Carolina; Bill Valdez, U.S. Department of Energy, Office of Science

Council Delegate: Marilee Long, Colorado State Univ.; Julie Ann Miller, D.C. Science Writers Assoc.

Geology and Geography

Chair Elect: W. Berry Lyons, Ohio State Univ.; Susan Trumbore, Univ. of California, Irvine

Member-at-Large of the Section Committee: Jill S. Baron, U.S. Geological Survey/Colorado State Univ.; John C. Mutter, Columbia Univ.

Electorate Nominating Committee: Sheryl Luzzadder Beach, George Mason Univ.; Mary Lynne Bird, American Geographical Society;

Kam-biu Liu, Louisiana State Univ.; Ellen Mosley-Thompson, Ohio State Univ.

History and Philosophy of Science
Chair Elect: William Bechtel, Univ. of California, San Diego; Alan J. Rocke, Case Western Reserve Univ.
Member-at-Large of the Section Committee: Paul Lawrence Farber, Oregon State Univ.; Silvan Sam Schweber, Brandeis Univ.
Electorate Nominating Committee: James R. Bartholomew, Ohio State Univ.; Rachelle D. Hollander, National Academy of Engineering/Univ. of Maryland; Brian Skyrms, Univ. of California, Irvine; Phillip R. Sloan, Univ. of Notre Dame

Industrial Science and Technology
Chair Elect: Laura A. Philips, independent consultant, New York, NY; S. Tom Picraux, Los Alamos National Laboratory
Member-at-Large of the Section Committee: Ray H. Baughman, Univ. of Texas at Dallas; Proctor Reid, National Academy of Engineering
Electorate Nominating Committee: Ilan Ben-Zvi, Brookhaven Natl. Lab.; Anthony Fainberg, Institute for Defense Analyses; Tingye Li, independent consultant, Boulder, CO; Robert W. Sprague, Rancho Palos Verdes, CA

Information, Computing, and Communication
Chair Elect: Bonnie C. Carroll, Information International Associates, Inc.; Edward D. Lazowska, Univ. of Washington
Member-at-Large of the Section Committee: Julia Gelfand, Univ. of California, Irvine; Benjamin Kuipers, Univ. of Texas at Austin
Electorate Nominating Committee: William Richards (Rick) Adrion, Univ. of Massachusetts Amherst; James D. Foley, Georgia Inst. of Technology; Clifford A. Lynch, Coalition for Networked Information; Eugene H. Spafford, Purdue Univ.
Council Delegate: Lewis M. Branscomb, Scripps Inst. of Oceanography; Maureen C. Kelly, consult-
Kuipers, Univ. of Texas at Austin
Electorate Nominating Committee: William Richards (Rick) Adrion, Univ. of Massachusetts Amherst; James D. Foley, Georgia Inst. of Technology; Clifford A. Lynch, Coalition for Networked Information; Eugene H. Spafford, Purdue Univ.
Council Delegate: Lewis M. Branscomb, Scripps Inst. of Oceanography; Maureen C. Kelly, consult-
ant, Haddonfield, NJ

Linguistics and Language Science
Chair Elect: Mark Liberman, Univ. of Pennsylvania; Annie Zaenen, Palo Alto Research Center
Member-at-Large of the Section Committee: Mark Aronoff, Stony Brook Univ.; Don Ringe, Univ. of Pennsylvania
Electorate Nominating Committee: Joan Maling, National Science Foundation; Sally McConnell-Ginet, Cornell Univ.; James Pustejovsky, Brandeis Univ.; Edward Stabler, Univ. of California, Los Angeles
Council Delegate: Stephen R. Anderson, Yale Univ.; Keren Rice, Univ. of Toronto

Mathematics
Chair Elect: Keith Devlin, Stanford Univ.; Martin Golubitsky, Univ. of Houston
Member-at-Large of the Section Committee: Alexander Nagel, Univ. of Wisconsin-Madison; Warren Page, City Univ. of New York
Electorate Nominating Committee: Harold P. Boas, Texas A&M Univ.; Maria-Carme Calderer, Univ. of Minnesota; Deborah F. Lockhart, National Science Foundation; Avy Soffer, Rutgers Univ.

Medical Sciences
Chair Elect: Christine A. Biron, Brown Univ.; Donald S. Burke, Univ. of Pittsburgh
Member-at-Large of the Section Committee: Jay A. Levy, Univ. of California San Francisco School of Medicine; Arlene H. Sharpe, Harvard Medical School
Electorate Nominating Committee: Harry B. Greenberg , Stanford Univ. School of Medicine; Margaret K. Hostetter, Yale School of Medicine; Thea D. Tlsty, Univ. of California San Francisco School of Medicine; Marsha Wills-Karp, Children's Hospital Medical Center, Univ. of Cincinnati

Neuroscience
Chair Elect: Mahlon R. DeLong, Emory Univ.; J. Anthony Movshon, New York Univ.
Member-at-Large of the Section Committee: Hollis T. Cline, Cold Spring Harbor Laboratory; Cheryl L. Sisk, Michigan State Univ.
Electorate Nominating Committee: Rosemarie Booze, Univ. of South Carolina; Eliot Brenowitz, Univ. of Washington; John F. Disterhoft, Northwestern Univ.; Charles D. Gilbert, Rockefeller Univ.

Pharmaceutical Science
Chair Elect: William E. Evans, St. Jude Children's Research Hospital; Kenneth Thummel, Univ. of Washington
Member-at-Large of the Section Committee: C. Anthony Hunt, Univ. of California, San Francisco; Dhiren Thakker, Univ. of North Carolina, Chapel Hill
Pharmaceutical Science
Chair Elect: William E. Evans, St. Jude Children's Research Hospital; Kenneth Thummel, Univ. of Washington
Member-at-Large of the Section Committee: C. Anthony Hunt, Univ. of California, San Francisco; Dhiren Thakker, Univ. of North Carolina, Chapel Hill
Electorate Nominating Committee: F. Douglas Boudinot, Virginia Commonwealth Univ.; Günter Hochhaus, Univ. of Florida; Uday B. Kompella, Univ. of Nebraska; Wei-Chiang Shen, Univ. of Southern California
Council Delegate: Jim Gallo, Temple Univ.; Patrick J. Sinko, Rutgers Univ.

Physics
Chair Elect: Bill R. Appleton, Univ. of Florida; Alan Chodos, American Physical Society
Member-at-Large of the Section Committee: C. Lewis Cocke, Kansas State Univ.; Gene D. Sprouse, American Physical Society
Electorate Nominating Committee: Orlando Auciello, Argonne National Laboratory; Richard L. Cohen, independent consultant, Novato, CA; Robert P. Redwine, Massachusetts Inst. of Technology; Antoinette (Toni) Taylor, Los Alamos National Laboratory

Psychology
Chair Elect: Jane Stewart, Concordia Univ.; Edward Taub, Univ. of Alabama at Birmingham
Member-at-Large of the Section Committee: Susan Goldin-Meadow, Univ. of Chicago; Elissa L. Newport, Univ. of Rochester
Electorate Nominating Committee: Jeffrey R. Alberts, Indiana Univ.; John P. Capitanio, Univ. of California, Davis; Merrill F. Garrett, Univ. of Arizona; Jeri S. Janowsky, Oregon Health & Science Univ.

Social, Economic, and Political Sciences
Chair Elect: Craig Calhoun, Social Science Research Council/New York Univ.; Karen S. Cook, Stanford Univ.
Member-at-Large of the Section Committee: Robert Jervis, Columbia Univ.; Judith M. Tanur, SUNY Stony Brook
Electorate Nominating Committee: Henry E. Brady, Univ. of California, Berkeley; Nancy M. Gordon, U.S. Census Bureau; Felice J. Levine, American Educational Research Association; Joyce Lewinger Moock, independent advisor, Larchmont, NY

Societal Impacts of Science and Engineering
Chair Elect: Dan Kammen, Univ. of California, Berkeley; Caroline S. Wagner, George Washington Univ.
Member-at-Large of the Section Committee: Kerri-Ann Jones, independent consultant, Castine, ME; M. Granger Morgan, Carnegie Mellon Univ.
Electorate Nominating Committee: Peter D. Blair, National Research Council; Thomas Dietz, Michigan State Univ.; Michele Garfinkel, J. Craig Venter Inst.; David M. Hart, George Mason Univ.; Charlotte Kuh, National Academies; William A. Stiles Jr., consultant, Norfolk, VA
Kerri-Ann Jones, independent consultant, Castine, ME; M. Granger Morgan, Carnegie Mellon Univ.
Electorate Nominating Committee: Peter D. Blair, National Research Council; Thomas Dietz, Michigan State Univ.; Michele Garfinkel, J. Craig Venter Inst.; David M. Hart, George Mason Univ.; Charlotte Kuh, National Academies; William A. Stiles Jr., consultant, Norfolk, VA
Council Delegate: Robert Cook-Deegan, Duke Univ.; Frank N. Laird, Univ. of Denver

Statistics
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Early Urban Development in the Near East

Jason A. Ur,[1]* Philip Karsgaard,[2] Joan Oates[3]

We present here the results of a study of the evolution of urbanism at the site of Tell Brak, in northeastern Syria. We approached demographic scale, density, and patterns of growth by using the spatial distribution of chronologically sensitive surface artifacts as a proxy indicator for the distribution and density of ancient settlement (*1*). Our results show Brak's urban origins to be contemporary with the appearance of cities in southern Iraq, the region generally considered to be the birthplace of Mesopotamian cities; hence, the emergence of urbanism in the Near East was a regionally multicentric process (*2*). The spatial patterning of its growth, however, diverges from the southern Mesopotamian model, with implications for underlying sociopolitical processes.

Urban growth at Brak began in the Late Chalcolithic (LC) 2 period [circa (c.) 4200 to 3900 calendar years before the common era (cal BCE)]. Ceramics from that time were found in six discrete clusters of 2 to 4 ha throughout the outer settlement complex, generally 200 to 500 m from the central mound (Fig. 1A). Also at that time, the central mound was entirely settled, and recent excavations have uncovered architecture and artifacts suggestive of social stratification (*3*). We calculated the total settled area at 55 ha, at a time when few contemporary settlements exceeded 3 ha. Thus, during the LC 2 period Brak witnessed the rapid formation of a spatially extensive settlement characterized by clusters of occupied space interspersed with vacant zones in the outer town.

During the early to mid-fourth millennium BCE (LC 3 to 4, 3900 to 3400 cal BCE, Fig. 1B), outer town settlement expanded inward. Many formerly unsettled areas were then filled. The central mound hosted large industrial structures and at least one elaborately decorated temple. The total LC 3 to 4 settled area grew to 130 ha. We interpreted the abundance of surface ceramics as an indicator of increased density of occupation. Thus, settlement density increased along with spatial extent. At this time, the largest of Brak's neighbors reached only 15 ha, and only one contemporary settlement in southern Mesopotamia, Uruk, exceeded it in size (*4*).

This trajectory of urban growth from 4200 to 3400 cal BCE must reflect changes in underlying social and political structures. The spatial separation between settlement clusters suggests social distance between discrete subcommunities. In this sense, they resembled an exploded form of the later nucleated Mesopotamian city, where neighborhoods were divided not by space but by walls and limited points of access. At Brak, clustering may have resulted from maintenance of social distance by immigrant groups. Existing social mechanisms may not have been able to sustain increased density in a nucleated form.

This dispersed pattern suggests both dependence on but some autonomy from the political power on the central mound. Previous research assumed that centralized and hierarchical sociopolitical institutions created cities as functional adaptations to problems of political and economic organization. Recently, however, archaeologists increasingly appreciate the bottom-up, or emergent, properties of ancient settlements (*5*, *6*). Elite coercion does not appear to be solely responsible for the initial development of urbanism at Brak. It seems likely that urbanism was at least in part the unintended result of the actions of autonomous and nonhierarchically ranked groups.

At the end of the fifth millennium BCE, a spatially extensive settlement emerged at Tell Brak, along the northern arc of the Fertile Crescent. It differed from the densely settled and nucleated urban forms of the succeeding Bronze Age in that it was composed of multiple discrete pockets of settlement surrounded by areas of low density or no settlement. Urbanism at Tell Brak began in a spatially extensive form, and its growth pattern was one of increasing density with simultaneous inward expansion. This pattern suggests a greater role for noncentralized processes in the initial growth of Brak and lesser importance for centralized authority; it also suggests that the study of Mesopotamian urbanism must accommodate multiple models for the origins of cities.

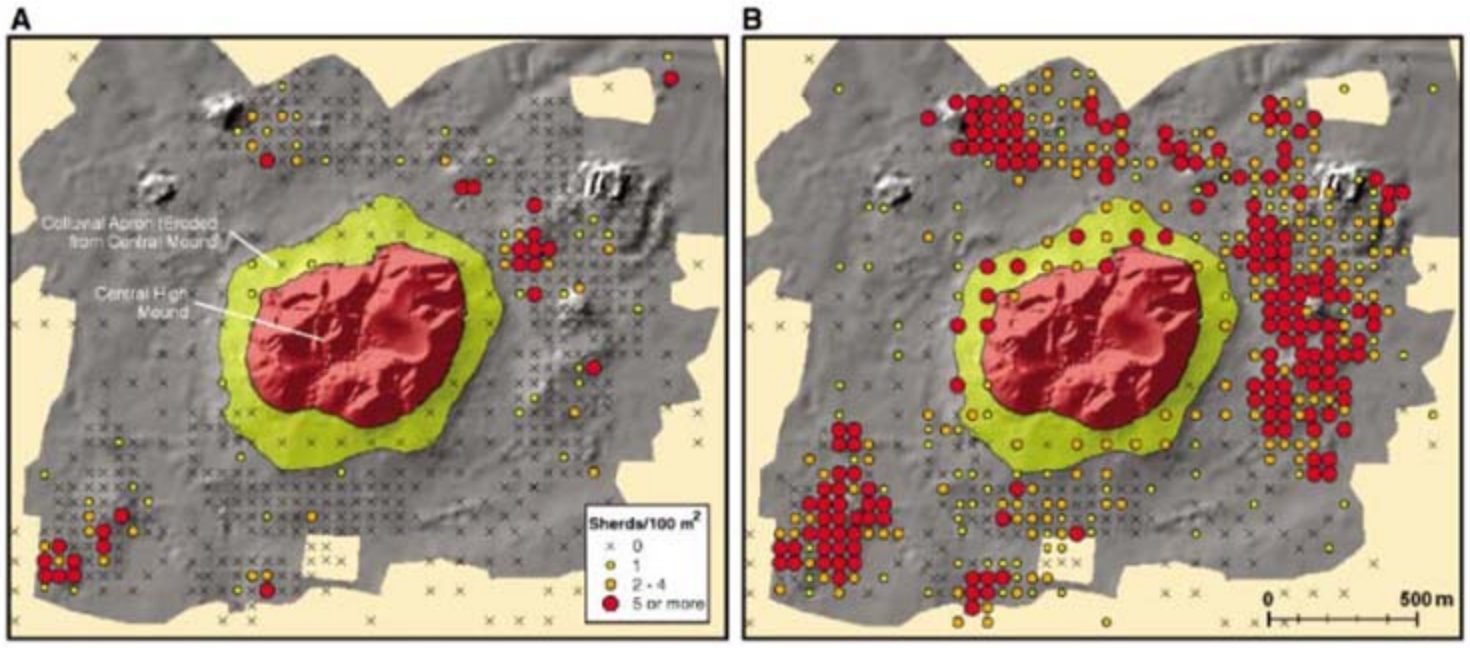

Fig. 1. Distribution of surface artifacts at Tell Brak, in 100-m² sherd collection units. (**A**) LC 2 (c. 4200 to 3900 BCE) ceramics; (**B**) LC 3 to 4 (c. 3900 to 3400 BCE) ceramics. Gray background represents hill-shaded topography.

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Epoxide-Opening Cascades Promoted by Water

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Selectivity rules in organic chemistry have been inferred largely from nonaqueous environments. In contrast, enzymes operate in water, and the chemical effect of the medium change remains only partially understood. Structural characterization of the "ladder" polyether marine natural products raised a puzzle that persisted for 20 years: Although the stereochemistry of adjacent tetrahydropyran (THP) cycles would seem to arise from a biosynthetic cascade of epoxide-opening reactions, experience in organic solvents argued consistently that such a pathway would be kinetically disfavored. We report that neutral water acts as an optimal promoter for the requisite ring-opening selectivity, once a single templating THP is appended to a chain of epoxides. This strategy offers a high-yielding route to the naturally occurring ladder core and highlights the likely importance of aqueous-medium effects in underpinning certain noteworthy enzymatic selectivities.

Brevetoxin B (Fig. 1, **1**), yessotoxin (**2**), the ciguatoxins, and related ladder polyether natural products are the active constituents of many harmful algal blooms, marine phenomena also known collectively as the red tide. Since the isolation and structural elucidation of **1** by Nakanishi and Clardy in 1981 (*1*), the distinctive molecular architecture and extreme lethality to marine life of these toxins continue to stimulate the development of methods for their chemical synthesis (*2*–*4*) and research into their mode of action (*5*).

How these molecules are assembled by the dinoflagellates that produce them has also been an active area of investigation (*6*–*8*) and, to be sure, speculation. Although they are among the most complex secondary metabolites ever characterized, all ladder polyethers possess a structural pattern and stereochemical regularity that confer upon them a certain degree of simplicity. A backbone of repeating oxygen–carbon–carbon (O–C–C) units extends from one end of the polyether network to the other [e.g., gymnocin B (**3**); Fig. 2A, red bonds and O atoms], regardless of the size of the intervening rings and of any functional groups present on the rings. The "ladder" topography is the consequence of consistently trans stereochemistry across the carbon-carbon bonds of the ring junctions, coupled with the relative syn configuration of adjacent junctions.

The Nakanishi cascade hypothesis. More than 20 years ago, Nakanishi put forth a hypothesis that accounts for these structural and stereochemical similarities—the transformation of a polyepoxide (e.g., **4**) into a ladder polyether via a series or "cascade" of epoxide-opening events (Fig. 2A). (*9*) The oxygen and two carbon atoms of each epoxide constitute the O–C–C backbone, and with the proviso that all of the ring openings proceed with inversion of configuration, the trans-syn topography is explained by this mechanism. That there is little evidence to support this two-decade-old hypothesis has not deterred efforts to emulate such cascades.

Despite its intellectual appeal, however, the hypothesis relies upon a ring-opening process generally regarded to be disfavored (Fig. 2B). With few exceptions, epoxide-opening reactions of this type favor the smaller heterocycle [e.g., a tetrahydrofuran (THF) likely arising from a spiro transition state], not the larger one [a tetrahydropyran (THP), from fused transition state] (*10*–*12*). Most of the approaches to promote the desired outcome use "directing groups" that must be covalently attached to the epoxides. (*13*) In contrast, catalytic antibodies (*14*) and transition-metal complexes (*15*, *16*) can be particularly effective in certain cases involving a single epoxide-opening event. To date, however, all existing THP-selective cascades that open more than one epoxide have required a directing group at every epoxide (*17*–*19*). These directing groups either are not found in the natural products or for other reasons clearly cannot be the natural solution. Therefore, though amenable to the synthesis of certain polyether ring systems, these methods do not provide evidence in support of or against the Nakanishi hypothesis.

Thus, if epoxide-opening reactions are used in ladder polyether biosynthesis, then how is this preference for the smaller ring overcome? Enzymatic control is a logical supposition, but there is as yet no evidence for such an intervention. With the joint aims of addressing this question and accelerating the synthesis of ladder polyethers, we have focused our recent efforts in this area on "directing-group-free," THP-selective cascades (*20*). Our approach stems from an analysis of the potential factors governing the regioselectivity of epoxide opening in these reactions and uses a template to modulate them in the desired manner.

We reasoned that in **5**, where one THP is already in place, entropic issues that might normally favor the undesired spiro transition state would be minimized and instead enthalpic contributions to the energies of the competing transition states would play a more important role (Fig. 2C). *Trans*-bicyclo[4.4.0]decane derivatives are typically less strained than their *trans*-bicyclo [4.3.0]nonane counterparts, and were this difference in developing ring strain reflected in the transition states, then the desired THP product (**6**) might be favored in this templated system under the appropriate reaction conditions.

Water as a reaction promoter. To test these hypotheses, we prepared **5** and exposed it to a wide range of combinations of acids, bases, solvents, and other additives (*21*). Bases tended to favor the THF product **7**, whereas acids exhibited a slight preference for the desired THP product (**6**). Combinations of acids and bases (Lewis or Brønsted) also favored **7**. To better understand the requirements for activation of the nucleophile and the electrophile, we examined the pH dependence of THP-to-THF selectivity [various buffers (e.g., phosphate, tris, His) and ionic strengths]. These experiments revealed a clear and provocative trend (Fig. 2D): In all cases, the selectivity for the desired THP product increases substantially as the pH of the reaction

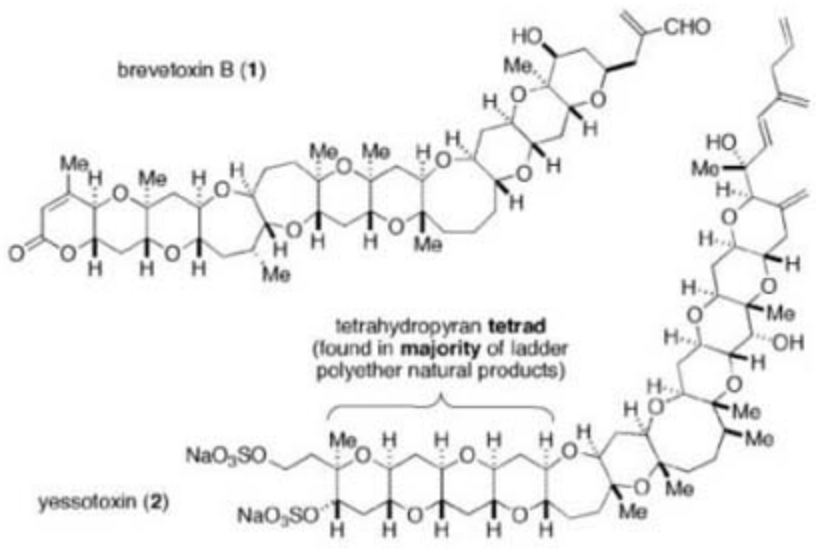

Fig. 1. Representative ladder polyether natural products. Me, methyl.

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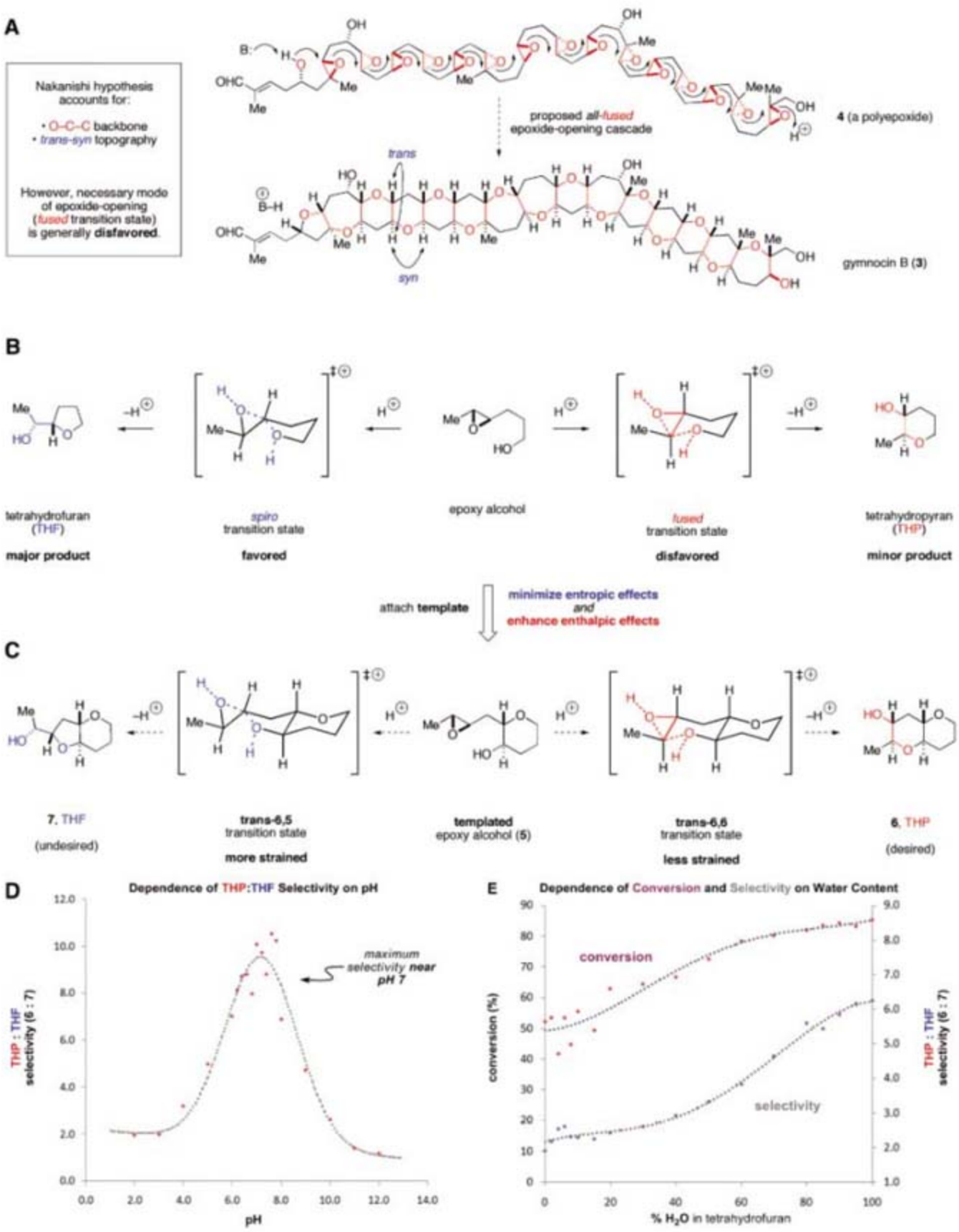


Fig. 2. (**A**) Structural and stereochemical patterns explained by the Nakanishi hypothesis of ladder polyether biosynthesis. (**B**) The two transition states (fused and spiro) and corresponding products for cyclization of an exemplary epoxy alcohol via epoxide opening. (**C**) Templated epoxide-opening cyclizations. (**D**) Dependence of THP:THF (**6**:**7**) selectivity on pH in cyclization of **5**. (**E**) Enhancement of conversion of **5** and of THP:THF selectivity by H_2O.

environment approaches neutrality, even exceeding 10:1 THP:THF selectivity near pH 7.

Several lines of evidence clearly implicate water in both the acceleration and increase in selectivity in these reactions. In less polar solvents (e.g., CH_2Cl_2 and toluene), low conversion of **5** is observed, and in polar aprotic solvents [e.g., CH_3CN, dimethyl sulfoxide, and *N*,*N*′-dimethylformamide (DMF)], although higher conversion to **6** and **7** occurs, the selectivity is greatly reduced (≤3:1 **6**:**7**). Furthermore, both increased THP:THF selectivity and increased conversion of **5** correlate with increased water content in the reaction milieu (Fig. 2E). Finally, deionized H_2O, in which both the ionic strength and percentage of impurities are near zero, provides the highest selectivity (>11:1 THP:THF). The only other promoters that we have found that approach the selectivity and rate exhibited by water are ethylene glycol (9:1) and methanol (8:1), which along with water can both provide and accept hydrogen bonds.

Water-promoted cascades. Having developed a THP-selective epoxide-opening method, we turned our attention to the possibility of using this approach in epoxide-opening cascades. However, we were well aware from our own work and from case studies reported by others that many highly selective epoxide ring-opening methods summarily fail when extended to cascades (*20*).

The synthesis of the epoxides is shown in Fig. 3A and emulates another aspect of Nakanishi's hypothesis, polyepoxidation of a polyene. Alkyne **8a** was extended to diyne **9a** and triyne **10a** in high yield by alkylation with the appropriate propargyl bromide (**11** and **12**, respectively). Alkyne **8b**, in which the hydroxyl group is protected as a silyl ether, was converted to alkynes **9b** and **10b** in the same manner and similar yield. Dissolving metal reduction (Li/NH_3) of **9a** provided a skipped diene (**13**) that was unstable enough to prohibit prolonged storage. The corresponding triene (not shown) from **10b** was even less robust, requiring hydroxyl protection before reduction.

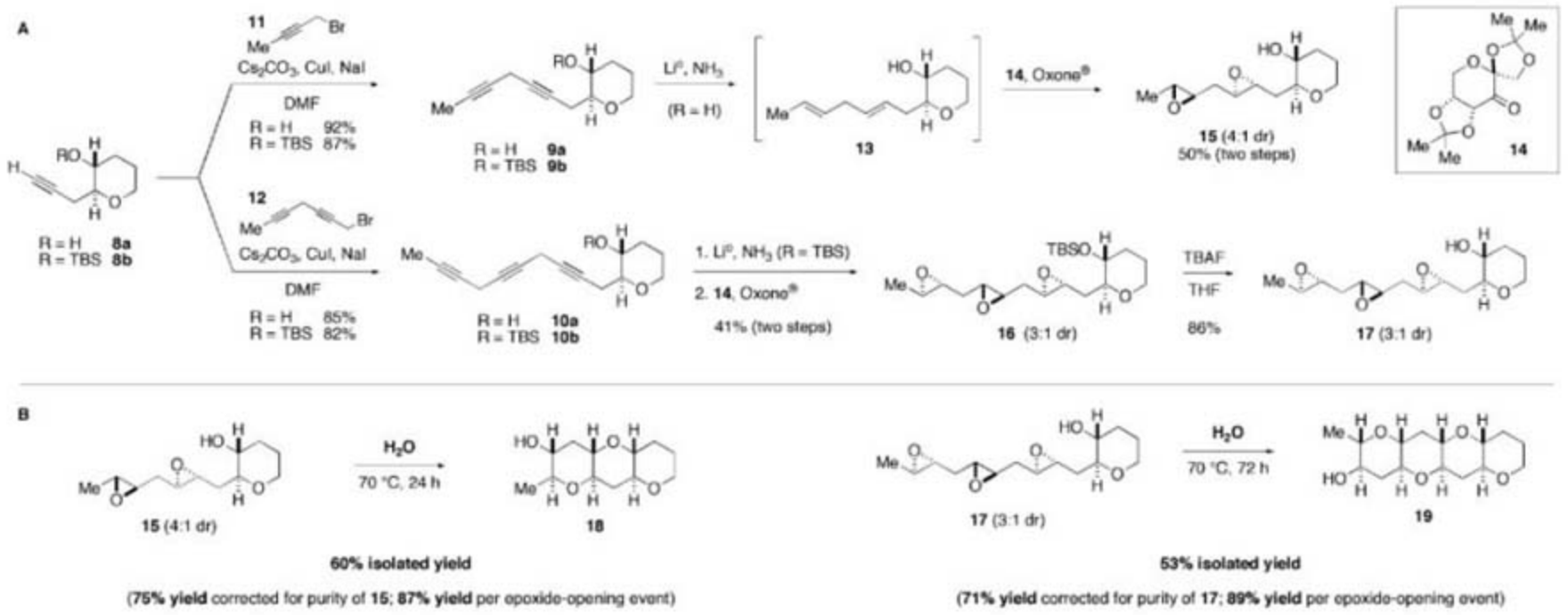
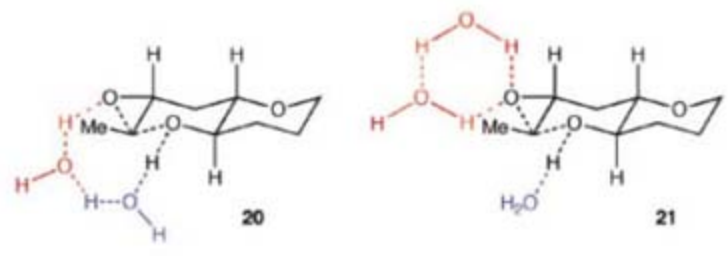
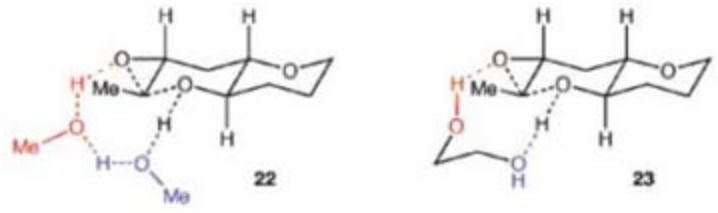


Fig. 3. (**A**) Synthesis of polyepoxides. (**B**) Epoxide-opening cascades promoted by H_2O. dr, diastereomeric ratio; DMF, dimethylformamide; TBS, *tert*-butyldimethylsilyl.

Fig. 4. Models of epoxide-opening reactions promoted by water (**20** and **21**), methanol (**22**), and ethylene glycol (**23**).





An epoxidation method developed by Shi that hinges upon fructose-derived ketone **14** and Oxone converted the diene and triene to the corresponding polyepoxides (**15** and **16**) (*22*). The moderate stereoselectivity appears to be due to the alkene proximal to the hydroxyl group; more remote alkenes do not suffer from this mismatched double diastereoselection. Diepoxide **15** and triepoxide **17** [after removal of the *tert*-butyldimethylsilyl (TBS) protective group] were obtained in 50% and 35% overall yield, respectively, from the diyne (**9a**) and triyne (**10b**).

The suboptimal stereochemical purity of **15** and **17** turned out to be of little concern (Fig. 3B). Heating **15** in deionized water for 24 hours at 70°C afforded a THP triad (**18**) in 60% isolated yield (75% yield when corrected for the purity of **15**). Similarly, a THP tetrad (**19**) representative of that found in more than half of the known ladder polyethers (Fig. 1) was obtained in 53% isolated yield (71% when corrected for the purity of **17**).

These THP-selective, epoxide-opening cascades are far higher-yielding than those that rely upon covalently attached directing groups. The per-epoxide yields of 87% (for **18**) and 89% (for **19**) are in line with the ~10:1 selectivity seen with monoepoxide **5** and do not change as a function of the number of epoxides or the number of THP rings preceding a given epoxide. In addition to validating the "template-by-a-THP" concept, this invariance would seem to support a mechanism for the cascade involving attack of an activated epoxide by the hydroxyl group attached to the preceding THP ring (right-to-left, as drawn in Fig. 3). The alternative mechanism (activated epoxide attacked by the next epoxide) has the opposite directionality (left to right) and is often invoked, even though it involves a highly strained epoxonium intermediate (*17*, *20*, *23*).

The effect of temperature on the reaction rate is substantial, but its impact on selectivity is minimal, consistent with the template concept of minimization of entropic contributions to the competing transition states. For example, about 1 month (28 days) was required for complete consumption of **17** at room temperature in pH 7.6 phosphate buffer (1.0 M), but polyether triad was nonetheless afforded in identical isolated yield (60%).

Mechanism and implications. Just as the development of all-THF epoxide-opening cascades (*24*, *25*) is taken as support of the Cane-Celmer-Westley hypothesis of monensin biosynthesis (*26*), we believe that the all-THP cascades herein represent long-sought evidence in favor of Nakanishi's hypothesis of ladder polyether biosynthesis (or at least the feasibility thereof) for several reasons: They are high yielding and highly THP-selective (yield per epoxide > 85% in all cases), require no directing groups on any of the epoxides, and are most effectively promoted by H_2O.

The template may be functioning as a surrogate for conformational constraints imposed by an enzyme active site, and because water is the superior promoter of the all-THP cascades, it is reasonable to propose that such cascades would be promoted by hydrogen-bond activation of the epoxide in the natural systems (*27*). Monensin and related polyethers are produced via epoxide ring-opening reactions promoted by epoxide hydrolases (EHs), and on the basis of sequence homology to other EHs, the epoxide appears to be activated by hydrogen bonds donated by two conserved tyrosine residues (*28*). Far less is known about brevetoxin and other ladder polyether toxins in this regard, but it is possible that dinoflagellates possess a similar set of polyketide synthase enzymes (*8*), though with epoxide hydrolases that are selective for the larger ring.

Water is one of the most heavily studied molecules, and its colligative structure and catalytic properties are still a subject of intense investigation (*29*–*31*). Thus, the means by which it affects selectivity in these cascades and organic reactions in general (*32*–*36*) is not without uncertainty. Moreover, although the reactions appear to be homogeneous, we cannot rule out surface effects or the formation of micelles that influence the

conformation and reactivity of the epoxy alcohols (**5**, **15**, and **17**). Nevertheless, as shown in Fig. 4 (**20**), activation of the nucleophile (OH group) and electrophile (epoxide) may be achieved by two water molecules (red and blue H_2O, respectively) in a cooperative network of hydrogen bonds that would account for not only the enhanced regioselectivity in water (relative to other solvents), but also the marginal effects of temperature on selectivity. Another possibility (**21**) is analogous to the dual-H-bond mode of activation (red H_2O) in epoxide hydrolases, but because activation of the electrophile is disconnected from that of the nucleophile, this model less easily explains the selectivity.

More complex hybrids that unite the attributes of these two models can also be posited, but at this stage we favor **20** for several reasons. Its relative simplicity (i.e., lower molecularity) constitutes a more easily testable structural hypothesis, and the results observed with methanol and ethylene glycol are also adequately explained, in the forms of **22** and **23**, respectively. Furthermore, as illustrated in **23**, ethylene glycol represents an attractive starting point for the development of small molecules that activate the nucleophile and electrophile in such a way as to effect cyclizations and cascades of even higher selectivity and efficiency. In the meantime, templated, water-promoted, THP-selective epoxide-opening cascades provide a straightforward means for efficient and rapid assembly of ladder polyethers, enabling investigations directed toward understanding the mode of action of these extraordinary natural products.

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Supporting Online Material

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REPORTS

Alfvén Waves in the Solar Corona

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Alfvén waves, transverse incompressible magnetic oscillations, have been proposed as a possible mechanism to heat the Sun's corona to millions of degrees by transporting convective energy from the photosphere into the diffuse corona. We report the detection of Alfvén waves in intensity, line-of-sight velocity, and linear polarization images of the solar corona taken using the FeXIII 1074.7-nanometer coronal emission line with the Coronal Multi-Channel Polarimeter (CoMP) instrument at the National Solar Observatory, New Mexico. Ubiquitous upward propagating waves were seen, with phase speeds of 1 to 4 megameters per second and trajectories consistent with the direction of the magnetic field inferred from the linear polarization measurements. An estimate of the energy carried by the waves that we spatially resolved indicates that they are too weak to heat the solar corona; however, unresolved Alfvén waves may carry sufficient energy.

Alfvén (*1*) first postulated the existence of oscillations of magnetized plasma in 1942. Of the three possible magnetohydrodynamic (MHD) wave modes, the slow and fast magnetoacoustic (MA) modes are compressible and susceptible to damping. The third so-called Alfvén mode is an incompressible transverse oscillation that propagates along field lines with magnetic tension as the restoring force. Following Alfvén's initial work, researchers soon realized that Alfvén waves could transport energy from the turbulent solar photosphere into the solar corona (*2*, *3*) and might explain one of the most important puzzles in solar physics: Why does the temperature of the solar atmosphere rise from 5000 to 2 million degrees Kelvin from the photosphere outward to the corona?

Over the past decade, the variety of wave phenomena observed in the solar corona has increased enormously. Transverse displacement

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oscillations associated with fast MA kink waves have been observed with the Transition Region and Coronal Explorer satellite (*4*, *5*). Intensity fluctuations associated with propagating slow-mode MA waves have been observed, with periods between 10 and 15 min in polar plumes with the Extreme Ultraviolet Imaging Telescope (EIT) on the Solar and Heliospheric Observatory (SOHO) (*6*) and in coronal loops with periods near 5 min in the extreme ultraviolet (*7*, *8*) and at visible wavelengths (*9*). High-frequency intensity oscillations have been seen during eclipses (*10*, *11*). Also, observations of coronal velocity fluctuations (*12*, *13*) have revealed waves with periods near 5 min.

Alfvén waves have been detected through in situ measurements of the solar wind for several decades (*14*); however, their definitive observation in coronal plasma is lacking for two reasons. First, Alfvén waves are incompressible, so they are not visible as intensity fluctuations; the intensity imagers used for most coronal observations will not see them. Second, velocity fluctuations inferred from Doppler shifts of emission lines require spectrograph or narrow-band filtergraph measurements; most coronal work has been performed with spectrographs that cannot observe over a large enough field of view in a time that is sufficiently short compared to the wave periods.

Here, we present results from the Coronal Multi-Channel Polarimeter (CoMP), a combination tunable filter and polarimeter that can measure properties of infrared coronal emission lines across a large field of view with short integration times [Supporting Online Material (SOM) text]. The CoMP instrument observes the complete polarization state of light through a 0.13-nm filter bandpass that is tuned to three wavelengths across the FeXIII coronal emission line at 1074.7 nm. The measured polarization state is parameterized by a Stokes vector [I, Q, U, V], where I is the intensity, Q and U describe net linear polarization states, and V describes the net circular polarization. Observations consisting of images of the corona between 1.05 and ~1.35 solar radii (R_{sun}) in the four Stokes parameters at the wavelengths 1074.52, 1074.65, and 1074.78 nm were obtained every 29 s on 30 October 2005 between 14.261 and 23.562 hours UT, with a spatial sampling of 4.5 arc sec per pixel.

After detector calibrations (SOM text), we determined the motion of the images during the day with a cross-correlation technique and translated the images to a common center. Lastly, the images were interpolated in time onto a grid with a constant spacing of 29 s. We selected a subarray of the data on the east limb for further analysis. This region included active region loops and a coronal cavity (Fig. 1A).

For each point in the selected subarray and each image in the time series, the central intensity of the line, the central wavelength, and the line width were obtained from a Gaussian fit to the intensity (Stokes I) at the three wavelengths. The line-of-sight (LOS) velocity was determined from the Doppler shift of the central wavelength from the rest wavelength of the emission line. Also, the degree of linear polarization, p, and the direction of the magnetic field (azimuth) in the plane of the sky (POS), ϕ, were obtained from Stokes I, Q, and U using only the central (1074.65-nm) bandpass from the relations

$$p = (Q^2 + U^2)^{1/2}/I \quad (1)$$

$$\phi = \tfrac{1}{2}\tan^{-1}(U/Q) \quad (2)$$

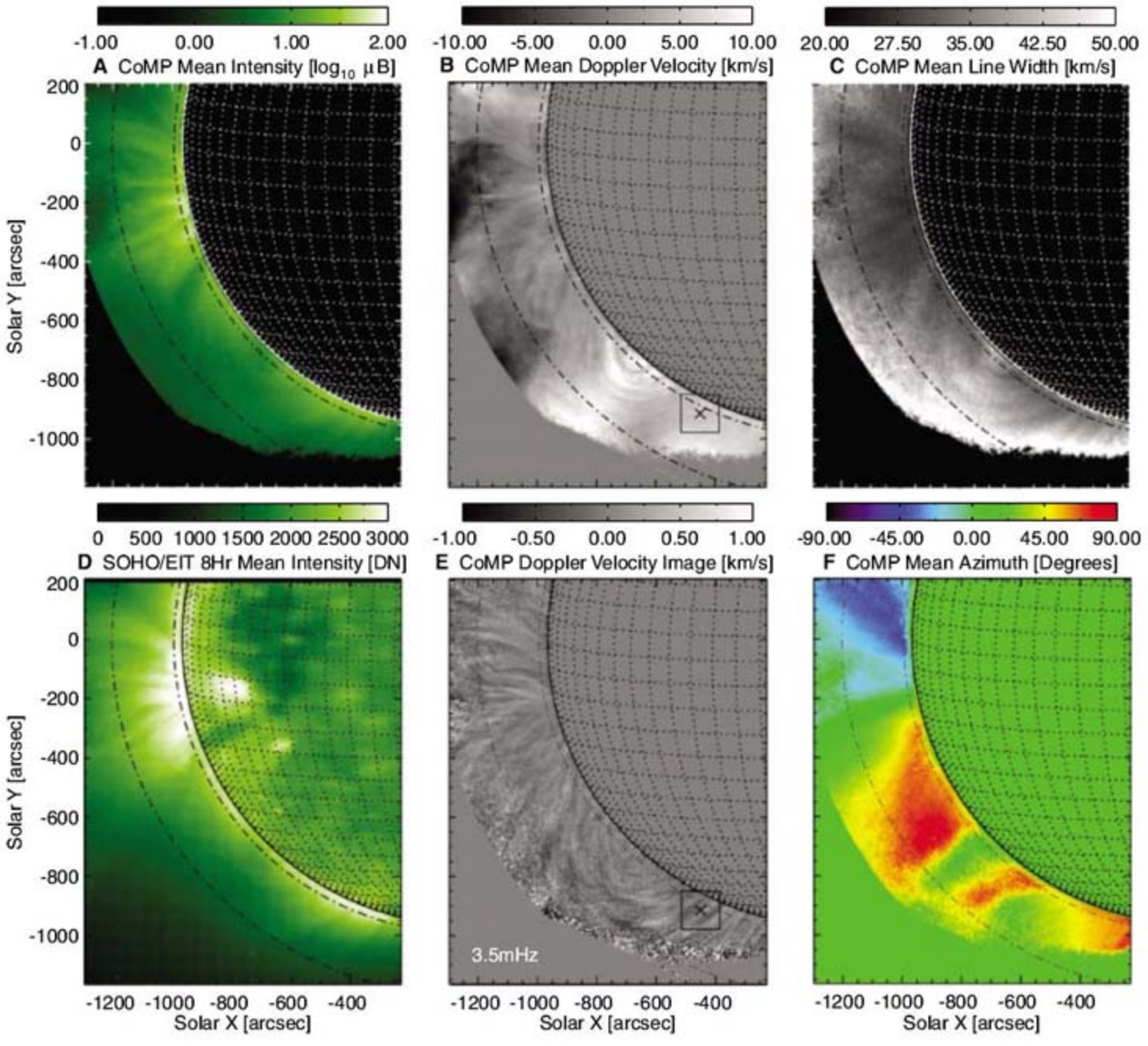

Fig. 1. From left to right, top to bottom, the CoMP observations of time-averaged intensity (**A**), Doppler velocity (**B**), line width (**C**), 3.5-mHz filtered Doppler velocity snapshot (**E**), and POS azimuth (**F**). In addition, we show the SOHO/EIT 19.5-nm image averaged over the same time (**D**). DN, data number (the unit of brightness). (B) and (E) include the location (X) and surrounding square region used in the example of the travel-time analysis. Dot-dashed lines representing distances of 5 and 25% of R_{sun} (above the limb) that are used as limits to our analysis are indicated.

where ϕ has the well-known ambiguity of 90° (*15*), which does not affect the conclusions of the following analysis.

A movie of the velocity images (movies S2 and S4) reveals ubiquitous quasi-periodic fluctuations with root means square amplitude of about 0.3 km s^{-1}. The time series of intensity images does not reveal appreciable variation with fractional fluctuations, $\Delta I/I < 3 \times 10^{-3}$. A Fourier analysis (Fig. 2) of the region of bright active region loops shows a significant, broad peak in the power spectrum of velocity fluctuations centered at ~3.5 mHz (5-min period) with a width of about 1 mHz. Such a peak is absent in the power spectrum of intensity fluctuations or line width. The background spectrum at low frequencies rises as 1/frequency^2 due presumably to instrumental noise and coronal evolution. We find that the observed spectrum of velocity power is remarkably similar to the power spectrum of photospheric 5-min oscillations, and we note that the frequency distribution of velocity power is nearly identical for both the coronal cavity and the active loop regions.

We adapted a phase travel-time analysis (*16*–*18*) to characterize the propagation characteristics of the wave modes observed in the CoMP velocity time series. The data were Fourier filtered in time with a Gaussian filter with a central frequency of 3.5 mHz and a width (1/e folding) of 0.4 mHz. We then formed the cross-correlation map of the filtered time series at a reference pixel with nearby pixels sufficient in number to capture all areas of high correlation. The cross-correlation function with neighboring pixels is a Gabor wavelet that yields information about the group and phase travel times of the fluctuation (*17*). We see (Fig. 3A) that the observed oscillations can have very long correlation lengths (the length of the oblong contour of high cross-correlation) and detectable widths. The "island" of high cross-correlation (CC > 0.5) also has a distinct direction that follows the apparent trajectory of the propagating wave, as seen in movies S2 and S4.

By using the island of high cross-correlation as a mask, we computed the correlation length, the correlation width, the phase speed of the propagation, and the propagation angle relative to solar north-south. We used the cross-correlation weighted least-squares fit to the points inside the island to estimate the propagation angle and its associated error. In addition, by isolating the phase travel times in the island and computing the distance of each pixel to the reference pixel, we estimated the phase speed (and standard error) of the wave from the least-squares fit of the distance and phase travel time. In the example shown in Fig. 3, we computed a correlation length of 45 Mm, a width of 9 Mm, a propagation trajectory of 46.2° (±4.0°), and a phase speed of 1.31 (±0.24) Mm s^{-1} at the reference pixel. Note that the measured phase speeds are POS projections and are therefore lower limits. This travel-time analysis was repeated, successively substituting all pixels between 1.05 and 1.25 R_{sun} (dot-dashed lines in Fig. 1) as the reference pixel, to extract the wave properties at each point (Fig. 4 and table S1).

The CoMP instrument can infer the POS azimuth of the coronal magnetic field through the linear polarization measurements and Eq. 2 (Fig. 1F). This angle is compared with the angle of wave propagation inferred from the travel-time analysis (Fig. 4B) in Fig. 4F. Despite the fact that LOS integrations may influence the two angles differently, the high degree of correlation in this plot demonstrates that the waves propagate along field lines.

We believe that the waves we observe are Alfvén waves, for the following three reasons. The observed phase speeds (~2 Mm s^{-1}) are much larger than the sound speed (~0.2 Mm s^{-1}), and therefore the waves are not slow MA mode waves. The spatiotemporal properties of the velocity oscillations and the linear polarization measurements show that these waves propagate along field lines, which would not be the case for fast MA mode waves. In addition, the associated intensity fluctuations are very small. A source of waves distributed across the solar surface would not produce the coherent spatial structures aligned with the magnetic field, which are present in the velocity data.

The presence of a 5-min signature is not surprising because fluctuations in the corona with periods near 5 min have been widely observed, as discussed above. There is a growing consensus that photospheric 5-min acoustic oscillation modes (p modes) escape into higher layers via interactions with surface magnetic fields. In the

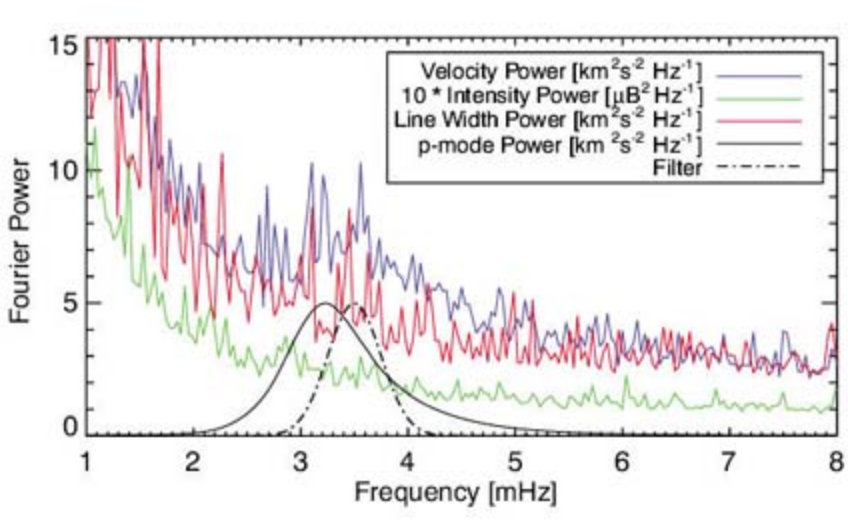

Fig. 2. Fourier power spectrum of the CoMP Doppler velocity (blue), intensity (green), and line width (red). Notice the significant, broad peak in the Doppler power spectrum centered on 3.5 mHz. We also show the (scaled) Gaussian filter applied in the analysis (dot-dashed black line) and the average power spectrum of intermediate degree photospheric oscillations (solid black line).

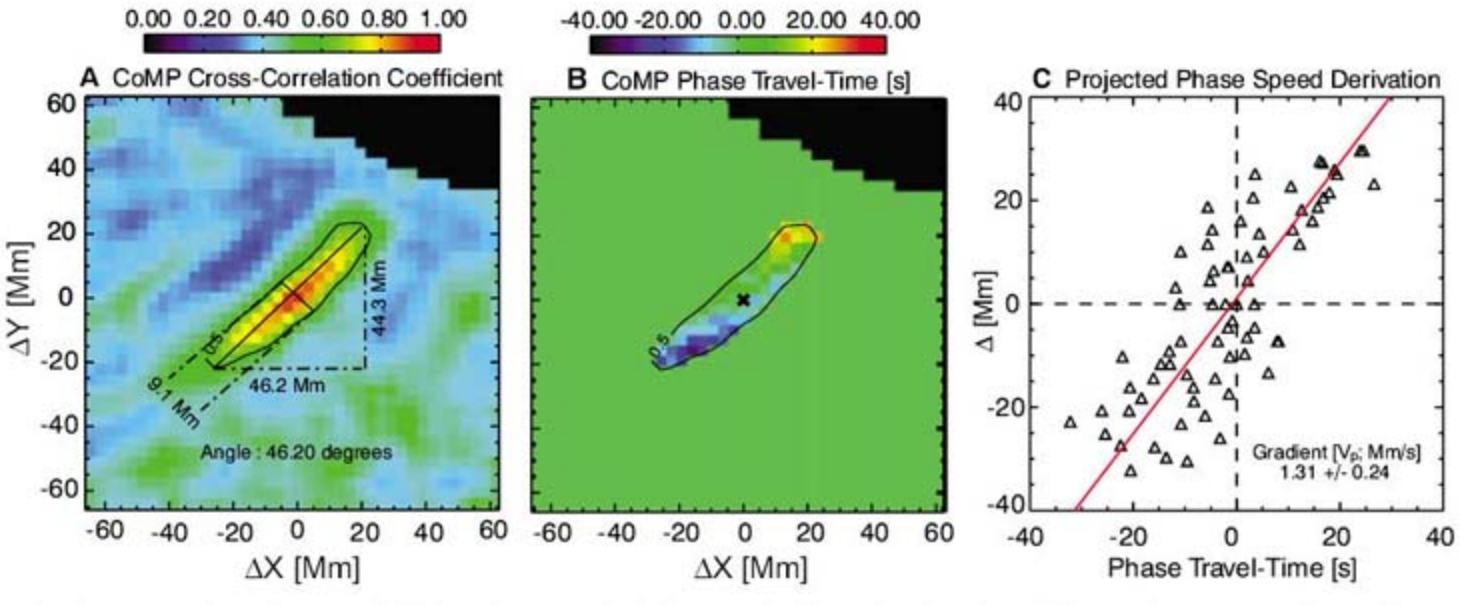

Fig. 3. Travel-time analysis of CoMP Doppler velocity measurements for the reference pixel (marked by the x) over the boxed region shown in Fig. 1. (**A**) The map of cross-correlation coefficients with a contour of 0.5, which is used to define the region used to determine the properties of the waves. (**B**) The map of computed phase travel times in the same region (the surrounding pixels are zeroed for clarity). (**C**) The relationship of phase travel time against the distance to the reference pixel; the phase speed of the wave in this region is estimated from a least-squares linear fit.

quiet Sun, these are rooted within the vertices and lanes defining the supergranular network. The internetwork nonmagnetic chromosphere tends to oscillate near 5 to 7 mHz in response to convective driving. In the network itself, the period shifts closer to 3 mHz (*19*). We observed (Fig. 2) that the CoMP velocity power spectrum peaks near 3.5 mHz, but relatively little of the 5-mHz power that dominates the internetwork chromosphere was evident. Perhaps the waves observed with CoMP originate from within the chromospheric network that forms the footpoints of the observed coronal loops. Recent work demonstrated that p modes with frequencies below the nominal acoustic cutoff frequency can leak into the upper chromosphere along magnetic field lines that are inclined to the gravitational field, effectively reducing the cutoff frequency (*20*–*24*). The bulk of the 5-mHz power does not penetrate the chromospheric canopy as compressive oscillation modes (*17*, *25*, *26*), and so these frequencies may not have a strong signature in the corona. The waves we observed were only those that could "tunnel" through the complex chromosphere-transition region along the magnetic field lines and then be converted near the $\beta = 1$ surface, where the plasma force balance transitions from gas dominated to magnetic field dominated to Alfvén modes. Unfortunately, the conversion mechanism is not understood or easily modeled, given the complex structure of the interface between the chromosphere and corona.

We observe a dominance of upward over downward wave propagation. Of all of the pixels with acceptable errors, only ~1% had a negative phase speed indicative of downward propagation. This suggests that the waves are converted or their energy is dissipated before they reach the opposite footpoint. Given the large curvature of the field lines over a typical wavelength, we would expect that conversion of Alfvén to MA modes would be efficient (*27*).

To evaluate the ability of these waves to heat the corona, we estimated the energy flux as

$$F_W = \rho \langle v^2 \rangle c_A \quad (3)$$

where ρ is the density, v is the velocity amplitude, and c_A is the Alfvén speed. Assuming a typical value of the electron density of 10^8 cm^{-3}, we estimate $\rho \sim 2 \times 10^{-16}$ g cm^{-3}. The flux of energy propagating in the observed waves is then

$$F_W \sim 10 \text{ erg cm}^{-2} \text{ s}^{-1} \text{ (0.01 W m}^{-2}\text{)} \quad (4)$$

Because we only observed the LOS velocity, this estimate can be multiplied by a factor of 2. Even so, the flux is 4 orders of magnitude too small to balance the radiative losses even of the quiet solar corona, ~100 W m^{-2} (*28*). The amplitude of the Alfvén waves that we observed may be significantly attenuated by averaging over many unresolved waves within our spatial resolution element and along the coronal LOS. The nonthermal component of coronal emission line widths is typically ~30 km s^{-1} and temporally invariant, which, if due to unresolved Alfvén waves, could provide a steady energy flux sufficient to heat the corona.

These waves are ubiquitous in space and time. This makes them ideal candidates for "coronal seismology" (*29*, *30*), wherein the Alfvén speed (wave phase speed) can be used to measure the strength of coronal magnetic fields through the relation:

$$c_A = B/\sqrt{4\pi\rho} \quad (5)$$

where B is the magnetic field strength and ρ is the plasma density. The phase speeds obtained in this study are a projection onto the POS, that is, the speed multiplied by $\sin(i)$, where i is the angle between the LOS and the direction of wave propagation. Then, given an estimate of the density, the measured phase speeds provide an

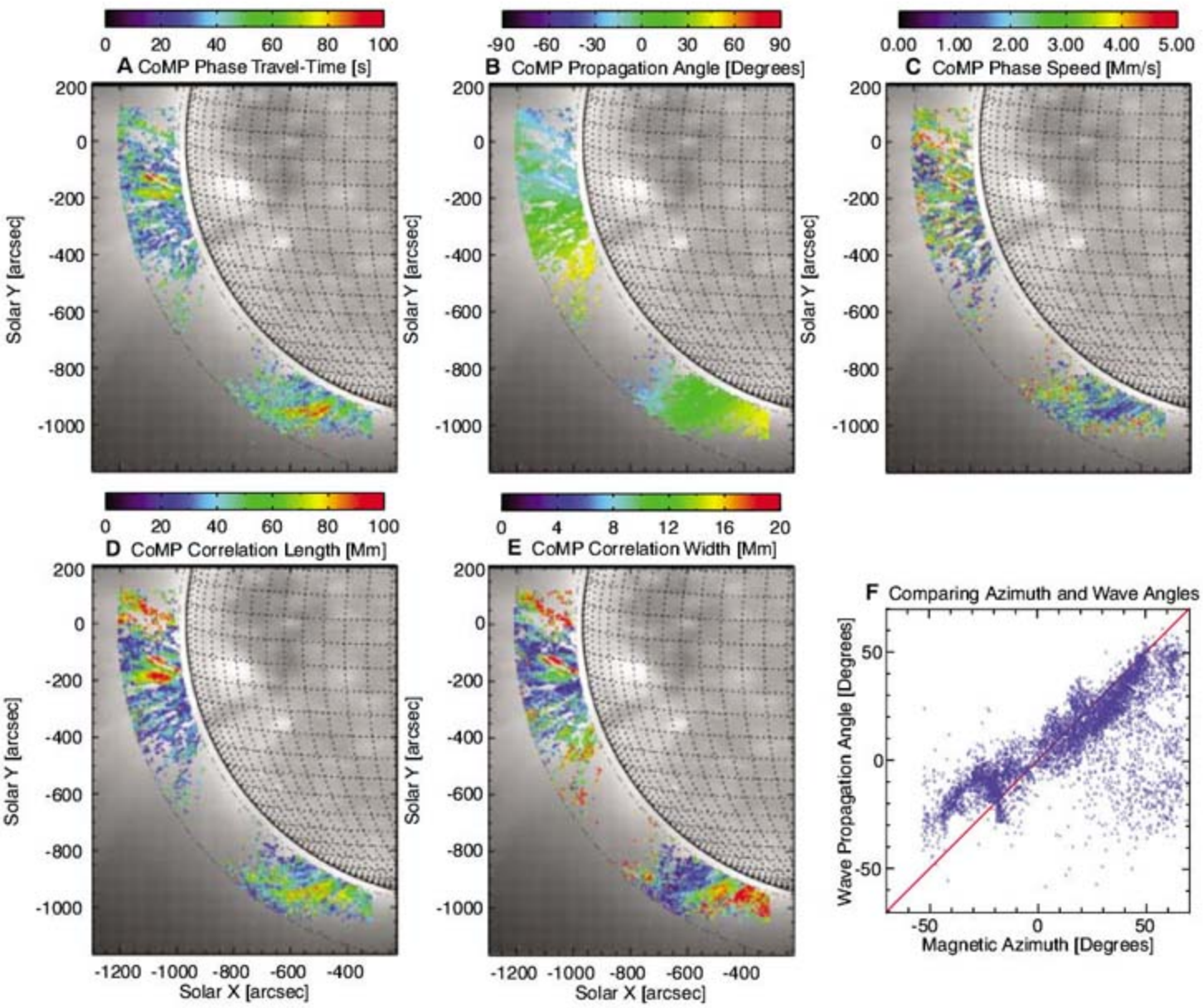

Fig. 4. The results of the CoMP travel-time analysis in the 1.05 to 1.25 R_{sun} range superimposed on the SOHO/EIT image from Fig. 1D. (**A** to **E**) The inferred wave travel time, propagation angle, phase speed, correlation length, and correlation width, respectively. Only points where the error in the phase speed from the regression analysis is less than 0.5 Mm s^{-1} and the error in the propagation angle is less than 10° are plotted. (**F**) The comparison of the inferred wave propagation angle and the measured magnetic field azimuth (Fig. 1F).

estimate of the POS component of the magnetic field. Assuming a typical electron density of 10^8 cm^{-3}, our measured phase speeds between 1.5 and 5 Mm s^{-1} correspond to projected magnetic field strengths between 8 and 26 G. We note that circular polarization measurements of coronal emission lines can provide an estimate of the LOS component of the magnetic field. Notably, seismology and polarimetry provide complementary projections of the coronal magnetic field, which can be combined to provide an estimate of both the strength and the inclination of the magnetic field. In future work, it will be possible to estimate the plasma density with CoMP observations through the intensity ratio of the FeXIII lines at 1074.7 and 1079.8 nm (*31*).

We have analyzed observations from the CoMP instrument that show an overwhelming flux of upward-propagating low-frequency waves throughout the solar corona. These waves propagate at speeds typical of Alfvén waves, and their direction of propagation mirrors the measured magnetic field direction. The waves we resolved do not have enough energy to heat the solar corona. We conclude that these ubiquitous waves are indeed Alfvénic and offer the real possibility of probing the plasma environment of the solar corona with a high degree of accuracy through coronal seismology.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5842/1192/DC1
Materials and Methods
Table S1
References
Movies S1 to S4

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Superconducting Interfaces Between Insulating Oxides

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At interfaces between complex oxides, electronic systems with unusual electronic properties can be generated. We report on superconductivity in the electron gas formed at the interface between two insulating dielectric perovskite oxides, $LaAlO_3$ and $SrTiO_3$. The behavior of the electron gas is that of a two-dimensional superconductor, confined to a thin sheet at the interface. The superconducting transition temperature of ≅ 200 millikelvin provides a strict upper limit to the thickness of the superconducting layer of ≅ 10 nanometers.

In pioneering work, it was demonstrated that a highly mobile electron system can be induced at the interface between $LaAlO_3$ and $SrTiO_3$ (*1*). The discovery of this electron gas at the interface between two insulators has generated an impressive amount of experimental and theoretical work (*2*–*8*), in part because the complex ionic structure and particular interactions found at such an interface are expected to promote novel electronic phases that are not always stable as bulk phases (*9*–*11*). This result also generated an intense debate on the origin of the conducting layer, which could either be "extrinsic" and due to oxygen vacancies in the $SrTiO_3$ crystal or "intrinsic" and related to the polar nature of the $LaAlO_3$ structure. In the polar scenario, a potential develops as the $LaAlO_3$ layer thickness increases that may lead to an "electronic reconstruction" above some critical thickness (*5*). Another key issue concerns the ground state of such a system; at low temperatures, a charge-ordered interface with ferromagnetic spin alignment was predicted (*4*). Experimental evidence in favor of a ferromagnetic ground state was recently found (*6*). Yet, rather than ordering magnetically, the electron system may also condense into a superconducting state. It was proposed that in field effect transistor configurations, a superconducting, two-dimensional (2D) electron gas might be generated at the $SrTiO_3$ surface (*12*). It was also pointed out that the polarization of the $SrTiO_3$ layers may cause the electrons on $SrTiO_3$ surfaces to pair and form at high temperatures a superconducting condensate (*13*, *14*). In this report, we explore the ground state of the $LaAlO_3/SrTiO_3$ interface and clarify whether it orders when the temperature approaches absolute zero. Our experiments provide evidence that the investigated electron gases condense into a superconducting phase. The characteristics of the transition are consistent with those of a 2D electron system undergoing a Berezinskii-Kosterlitz-Thouless (BKT) transition (*15*–*17*). In the oxygen vacancy scenario the observation of superconductivity provides a strict upper limit to the thickness of the superconducting sheet at the $LaAlO_3/SrTiO_3$ interface.

The samples were prepared by depositing $LaAlO_3$ layers with thicknesses of 2, 8, and 15 unit cells (uc) on TiO_2-terminated (001) surfaces of $SrTiO_3$ single crystals (*5*, *18*). The films were grown by pulsed laser deposition at 770°C and 6×10^{-5} mbar O_2, then cooled to room temperature in 400 mbar of O_2, with a 1-hour oxidation step at 600°C. The fact that only heterostructures with a $LaAlO_3$ thickness greater than three uc conduct (*5*) was used to pattern the samples (*19*). Without exposing the $LaAlO_3/SrTiO_3$ interface to the environment, bridges with widths of 100 μm and lengths of 300 μm and 700 μm were structured for four-point measurements, as well as two-uc-thick $LaAlO_3$ layers for reference (*18*).

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Transmission electron studies (*18*) were performed on reference samples grown under conditions identical to those described above. Cross-sectional cuts were prepared by mechanical polishing followed by low-energy, low-angle ion milling and investigated by scanning transmission electron microscopy (STEM) (*18*). Figure 1A shows a high-angle annular dark field (HAADF) STEM image of the sharp interface between a 15-uc-thick $LaAlO_3$ film and the $SrTiO_3$ substrate. The film is found to be coherent with the substrate with no obvious defects or dislocations at the interface, resulting in biaxial tensile strain of ≅ 3%, as measured from STEM images (*18*). The out-of-plane lattice constant of the $LaAlO_3$ film is ≅ 3.78 Å, which is close to the bulk value and suggests either a rather small Poisson ratio as previously reported (*20*) or out-of-plane relaxation in the thin film (*21*). To obtain an upper limit on the extent of electronic structure and compositional changes below the interface, electron energy-loss spectroscopy (EELS) in the STEM was used to probe the chemistry of the heterostructure at the atomic scale. Simultaneously recorded O-K and Ti-$L_{2,3}$ edges close to and far away from the interface are shown in Fig. 1, B and C. By 1.5 nm away from the interface, the changes in the O-K edge are very slight, suggesting an upper limit to the oxygen vacancy concentration of 3%. At 6 nm away from the interface, the changes in the O-K and Ti-$L_{2,3}$ edges compared with bulk $SrTiO_3$ fall below the noise level (<1% oxygen vacancy concentration). The small changes of the Ti-$L_{2,3}$ edges are consistent with a slight increase in Ti^{3+}, either from oxygen deficiency (*22*) or a compensating interface charge (*18*).

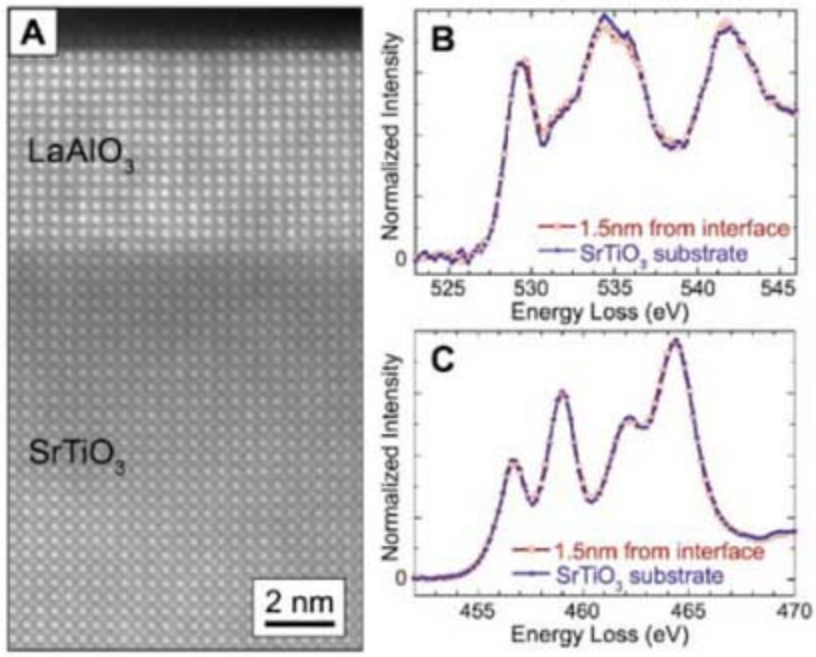

Fig. 1. STEM and EELS analysis of a $LaAlO_3/SrTiO_3$ heterostructure. (**A**) High-angle annular dark field image of a 15-uc-thick $LaAlO_3$ film grown on $SrTiO_3$ showing a coherent interface. (**B**) O-K EELS spectra of the $SrTiO_3$ close to (1.5 nm) and far away from the interface. Even at 1.5 nm from the interface, the O-K fine structure is only very slightly damped compared with the bulk. The damping could be caused by the presence of a low concentration of oxygen vacancies. (**C**) Small changes of the Ti-$L_{2,3}$ fine structure close to the interface are consistent with a small concentration of Ti^{3+}, which falls below the detection limit by 6 nm from the interface and beyond.

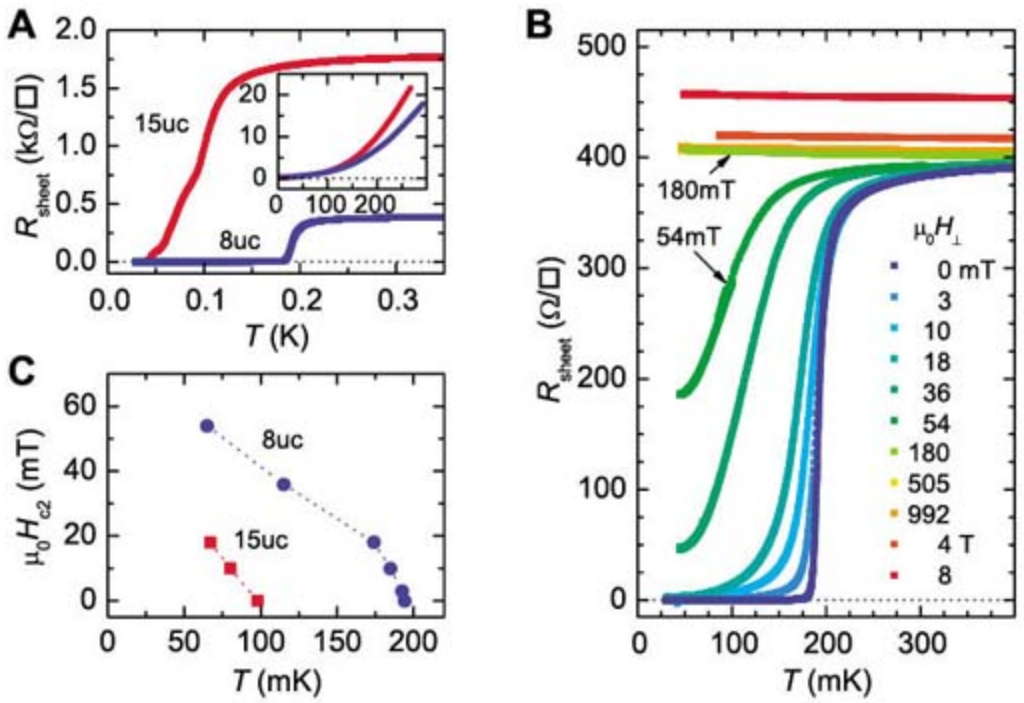

Fig. 2. Transport measurements on $LaAlO_3/SrTiO_3$ heterostructures. (**A**) Dependence of the sheet resistance on T of the 8-uc and 15-uc samples (measured with a 100-nA bias current). (Inset) Sheet resistance versus temperature measured between 4 K and 300 K. (**B**) Sheet resistance of the 8-uc sample plotted as a function of T for magnetic fields applied perpendicular to the interface. (**C**) Temperature dependence of the upper critical field H_{c2} of the two samples.

Two samples were analyzed by transport measurements and found to be conducting (Fig. 2A), their 2-uc-thick control structures being insulating (resistance $R > 30$ MΩ) at all temperatures T (32 mK < T < 300 K). At T ≅ 4.2 K, the Hall carrier densities of the 8-uc and 15-uc samples equal ≅ 4×10^{13}/cm^2 and ≅ 1.5×10^{13}/cm^2, and the mobilities ≅ 350 cm^2/Vs and ≅ 1000 cm^2/Vs, respectively. Whether the differences in the sample properties present an intrinsic effect that is caused by the variation of the $LaAlO_3$ thickness remains to be explored. The Hall response is only weakly temperature dependent [Hall resistance R_H(300 K)/R_H(4.2 K) ≅ 0.8 and 0.95 for the 8-uc and 15-uc samples, respectively]. Magnetic fields up to $\mu_0 H = 8$ T were applied to the 8-uc-thick sample, revealing a positive magnetoresistance. The samples investigated here do not show a hysteretic magnetoresistance. No minimum is found in the $R(T)$ characteristics of the 8-uc sample, such as was reported recently for $LaAlO_3/SrTiO_3$ samples fabricated under different conditions (*6*). For the 15-uc sample, a shallow minimum in the $R(T)$ curve was observed at 4 K.

At ≅ 200 mK and ≅ 100 mK, respectively, the 8-uc and 15-uc samples undergo a transition into a state for which no resistance could be measured (Fig. 2A). The widths of the transitions (20% to 80%) of the 8-uc and 15-uc samples are ≅ 16 mK and ≅ 51 mK, respectively. The resistance drops by more than three orders of magnitude to below the noise limit of the measurement (*18*). Application of a magnetic field $\mu_0 H$ = 180 mT perpendicular to the interface completely suppresses this zero-resistance state (Fig. 2B). Figure 3A displays the voltage versus current (V-I) characteristics of a bridge in the 8-uc sample, measured using a dc technique. At low temperatures, the V-I characteristics show a well-defined critical current I_c. The occurrence of the zero-resistance state and the characteristic $R(T,H)$ and $V(I,H)$ dependencies provide clear evidence for superconductivity.

The $T_c(H)$ dependence, where T_c is defined as $R(T_c) = 0.5 \times R(1\text{ K})$, provides a measure for the upper critical field $H_{c2}(T)$. The $H_{c2}(T)$ curve is shown in Fig. 2C; H_{c2}(0 K) ≅ 65 mT and ≅ 30 mT for the 8-uc and 15-uc samples, corresponding to coherence lengths ξ(0 K) ≅ 70 nm and ≅ 105 nm, respectively. Figure 3B shows the temperature dependence of the critical currents per unit width. The maximal values of I_c are 98 μA/cm and 5.6 μA/cm for the 8-uc and 15-uc samples, respectively. A steplike structure in the $V(I)$ curves displayed by the 15-uc sample (not shown) indicates that the low I_c of this sample is caused by inhomogeneities. Just below I_c, the

samples develop a small voltage drop which is proportional to the current and increases with temperature. As Fig. 4A shows for the 8-uc-thick sample, at 30 mK the associated resistance is at least four orders of magnitude smaller than the normal state resistance. With T increasing from 30 mK to 180 mK, the resistance grows exponentially from $\cong 0.1\ \Omega$ to $10\ \Omega$. Between 180 mK and T_c, the step at I_c disappears and power-law type $V(I)$ curves are measured.

Is the bulk of the $SrTiO_3$ superconducting or is it only a thin sheet at the interface layer? How thick is the superconducting layer? If the heterostructures were 2D superconductors, the transition into the superconducting state would be a BKT transition, characterized by a transition temperature T_{BKT} at which vortex-antivortex pairs unbind (*23*). A simple estimate of T_{BKT}, assuming that the sheet superconducting carrier density equals $4 \times 10^{13}/cm^2$, would suggest that in the samples, the BKT and mean field temperatures almost coincide. However, in case of large vortex fugacity, a high density of vortex-antivortex pairs is thermally generated and an ionic-like vortex-antivortex crystal is formed (*24*). For such a system, the melting of this lattice represents the BKT transition, which then occurs at lower temperatures. At the BKT transition, the current-induced Lorentz force causes dislocation-antidislocation pairs to unbind, resulting in a $V \propto I^a$ behavior, with $a(T_{BKT}) = 3$.

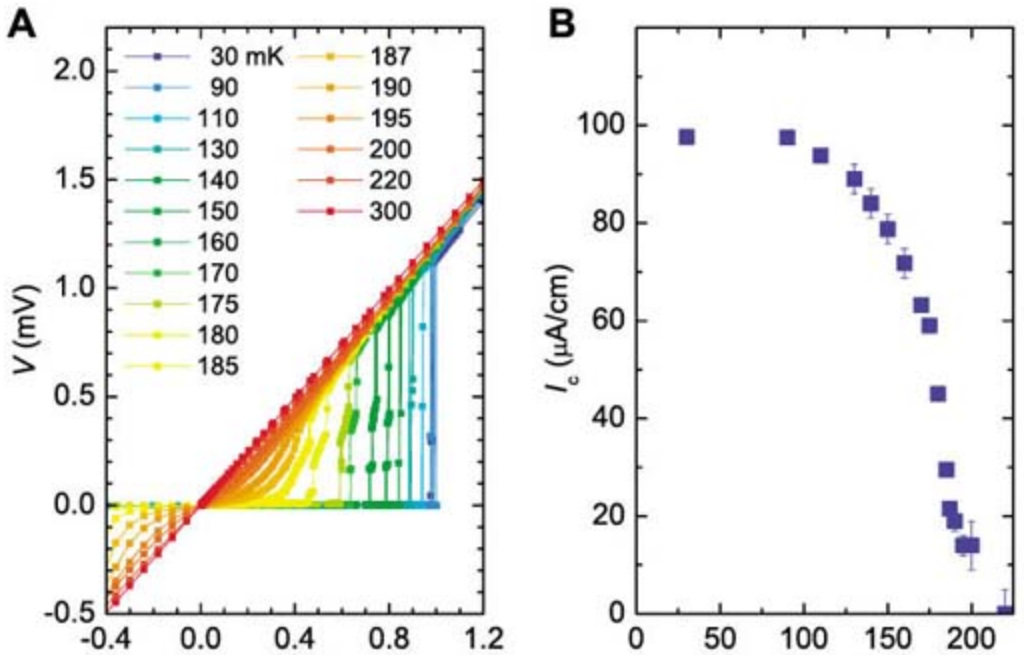

Fig. 3. $V(I)$ measurements of the 8-uc $LaAlO_3/SrTiO_3$ heterostructure. (**A**) Temperature-dependent voltage-current characteristics of a $100 \times 300\ \mu m^2$ bridge. (**B**) Measured temperature dependence of the linear critical current density, as obtained from (A).

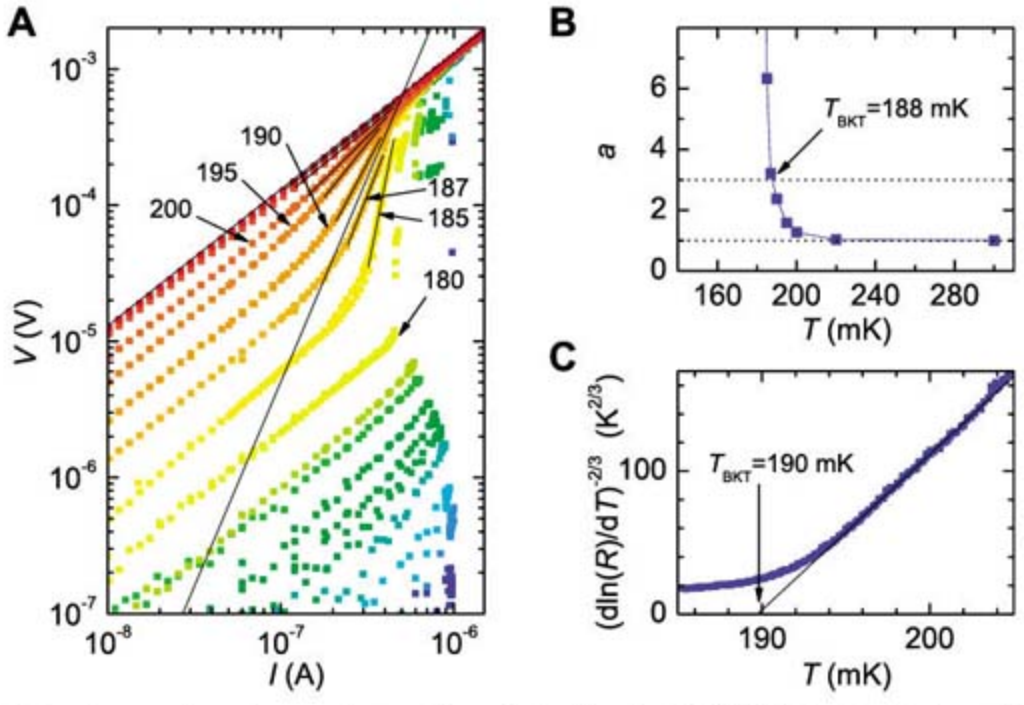

Fig. 4. Low-temperature transport properties of the 8-uc $LaAlO_3/SrTiO_3$ heterostructure. (**A**) $V(I)$ curves on a logarithmic scale. The color code is the same as that in Fig. 3A. The numbers provide the value of T, measured in mK, at which the curves were taken. The short black lines are fits of the data in the transition. The two long black lines correspond to $V = RI$ and $V \sim I^3$ dependencies and show that $187\ mK < T_{BKT} < 190\ mK$. (**B**) Temperature dependence of the power-law exponent a, as deduced from the fits shown in (A). (**C**) $R(T)$ dependence of the 8-uc sample ($I = 100$ nA), plotted on a $[d\ln(R)/dT]^{-2/3}$ scale. The solid line is the behavior expected for a BKT transition with $T_{BKT} = 190$ mK.

The samples indeed show clear signatures of the BKT behavior, such as a $V \propto I^a$ power-law dependence (Fig. 4A). As revealed by Fig. 4B, at $T = 188$ mK, the exponent a approaches 3; this temperature is therefore identified as T_{BKT}. The $V(I,T)$ characteristics (Fig. 4A) are very similar to the results of simulations treating finite-size 2D systems (*25*). The ohmic regime observed below T_{BKT} at small currents is expected for finite size samples and agrees quantitatively with an analysis (*18*) based on (*24*).

In addition, the $R(T)$ characteristics are consistent with a BKT transition, for which, close to T_{BKT}, a $R = R_0 \exp(-bt^{-1/2})$ dependence is expected (*26*). Here, R_0 and b are material parameters and $t = T/T_{BKT} - 1$. As shown by Fig. 4C, the measured $R(T)$ dependence is consistent with this behavior and yields $T_{BKT} \cong 190$ mK, in agreement with the result of the a-exponent analysis. The superconducting transition of the samples is therefore consistent with that of a 2D superconducting film. Hence, the superconducting layer is thinner than $\xi \cong 70$ nm.

Analysis of the superconducting transition temperature provides an independent bound on the layer thickness. If the superconductivity were due to oxygen defects in $SrTiO_{3-x}$, a carrier density of $\gtrsim 3 \times 10^{19}/cm^3$ would be required for a T_c of 200 mK (*27*). The measured sheet carrier densities thus give an upper limit for the thickness of the superconducting sheet of $\cong 15$ nm. Considering that the carrier concentration of the $SrTiO_{3-x}$ layer cannot be constant but has to conform to a profile following Poisson's equation as treated with consideration to the field-dependent $SrTiO_3$ susceptibility (*28*), one can set an upper limit for the thickness of the superconducting sheet of $\cong 10$ nm, a value much smaller than that suggested in (*7*, *8*) for the thickness of the conducting layer in reduced $LaAlO_3/SrTiO_3$ heterostructures. The carrier density profile at interfaces in oxygen-deficient $SrTiO_{3-x}$ has also been calculated in (*8*). As a result of this model, a sheet carrier density $> 5 \times 10^{14}/cm^2$ is needed to provide a carrier concentration of $3 \times 10^{19}/cm^3$. Because the sheet carrier densities of our samples equal only 1.5 to $4 \times 10^{13}/cm^2$, according to this model the superconductivity of the $LaAlO_3/SrTiO_3$ interface cannot be caused by doped $SrTiO_{3-x}$ alone.

The experiments presented here do not allow us to determine whether the observed superconductivity is due to a thin doped $SrTiO_3$ sheet or a novel phenomenon occurring at this artificial interface. Although the T_c of the heterostructures falls in the transition range of oxygen-deficient $SrTiO_{3-x}$, the transport properties of the samples differ to some extent from the ones of doped

$SrTiO_3$. Whereas in oxygen-deficient $SrTiO_{3-x}$ and Nb-doped $SrTiO_3$ films the Hall constant increases markedly below 100 K (*29*), it is less temperature dependent in $LaAlO_3/SrTiO_3$ heterostructures. In addition, the upper critical field of the heterostructures is an order of magnitude smaller than that of Nb-$SrTiO_3$ with the same T_c. Finally, our observation of both superconducting and insulating behavior on the same sample, depending on the precise $LaAlO_3$ layer thickness, is very hard to reconcile with a pure oxygen vacancy scenario.

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Large Magnetic Anisotropy of a Single Atomic Spin Embedded in a Surface Molecular Network

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Magnetic anisotropy allows magnets to maintain their direction of magnetization over time. Using a scanning tunneling microscope to observe spin excitations, we determined the orientation and strength of the anisotropies of individual iron and manganese atoms on a thin layer of copper nitride. The relative intensities of the inelastic tunneling processes are consistent with dipolar interactions, as seen for inelastic neutron scattering. First-principles calculations indicate that the magnetic atoms become incorporated into a polar covalent surface molecular network in the copper nitride. These structures, which provide atom-by-atom accessibility via local probes, have the potential for engineering anisotropies large enough to produce stable magnetization at low temperatures for a single atomic spin.

Magnetic structures with only a few atomic spins, such as single atoms and clusters on metal surfaces (*1*, *2*) and molecular magnets (*3*–*5*), can exhibit anisotropies that are large enough to maintain a stable spin orientation at low temperatures. The large anisotropies per each atom in these small clusters are of interest as a possible way to shrink magnetic bits below the size at which domains in current thin-film magnetic materials become unstable at room temperature. The impending approach of this superparamagnetic limit (*6*) threatens to halt the decades-long trend toward ever higher storage densities in magnetic memory. Besides this technological relevance, atomic-scale magnetic structures are also of great scientific interest because they exhibit intriguing quantum effects (*7*–*9*) and have the potential to be harnessed for quantum computing (*10*, *11*). Access to individual magnetic nanostructures by electronic transport measurements is possible with the use of electromigration junctions (*12*, *13*) and local probes (*2*, *14*–*18*). Whereas nanoscale junction devices may be more readily adapted to practical applications, studies using local probes provide an understanding of the nanomagnet's local environment, the crucial determinant of atomic-scale anisotropy.

Here we describe magnetic nanostructures with large magnetic anisotropy that can be individually constructed, studied, and manipulated with atomic-scale precision. Individual Fe or Mn atoms were placed at the desired locations on a CuN surface by manipulation with a scanning tunneling microscope (STM) tip. Our calculations indicate that the Fe and Mn atoms are embedded into a molecular network of polar covalently bonded Cu and N atoms within the CuN surface. Incorporation into the surface results in substantial charge transfer and distribution of spin polarization away from the magnetic atom and into the molecular network. We found that inelastic excitations of the atomic spin (*14*, *15*) are very prominent in the electron tunneling from an STM tip through the individual magnetic nanostructures. Changes in the spin-excitation energies as a magnetic field was applied along three orthogonal axes directly yielded both the strength and orientation of axial and transverse magnetic anisotropy for a single magnetic atom. The relative intensities of these inelastic excitations are well-described by a spin-transition matrix element that is analogous to that found in inelastic neutron scattering. These nanomagnetic systems combine large magnetic anisotropies with the flexibility that comes from being accessible on a surface by a local probe (*2*, *14*–*18*) and the potential for control of the magnetic properties previously available only in molecular magnets. This has great promise because, in the absence of transverse anisotropy, the single Fe atom on CuN would have an energy-reversal barrier similar in magnitude to that observed for atomic spins in the most anisotropic configurations in molecular magnets (*4*) and on metal surfaces (*1*).

Experiments were conducted with an ultrahigh-vacuum low-temperature STM with a base temperature of 0.5 K. We measured the differential conductance dI/dV using lock-in detection of the

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tunnel current I by adding a 20- to 50-μV_{rms} modulation at ~800 Hz to the sample bias voltage V [we used the root mean square (rms) amplitude for the modulation voltage]. The STM head was mounted in the cold bore of a split-coil magnet with magnetic fields B up to 7 T. The orientation of the magnet could be changed so that the magnetic field was applied either perpendicular to or in the plane of the crystal surface (*19*).

We used a single atomic layer of CuN (*20*) to decouple the spin of the magnetic atoms from the conduction electrons in the underlying Cu(100) surface (*15*). A small island of CuN with an adsorbed Fe atom is shown in Fig. 1A. As seen in the cross section, the Fe atom has a large apparent height of 2.6 Å, which indicates that electronic tunneling through the atom is almost three orders of magnitude greater than it is through the bare CuN. The spatial resolution of the STM images, particularly the observation of single rows of missing N atoms such as those shown in Fig. 1A, allowed us to overlay the lattice structure and determine the binding site of the atom and its local environment: In Fig. 1A, the Fe is on top of a Cu atom with two N atoms as its horizontal nearest neighbors (*21*).

To understand the structure formed by magnetic atoms on the CuN surface, we calculated the electronic structure using the all-electron full-potential linearized augmented plane wave method of density functional theory (DFT) (*22*) with the exchange-correlation potential in the generalized gradient approximation (GGA) (*23*). Figure 1B shows cross sections of the calculated charge density for a single layer of CuN on Cu(100) (*24*) along two orthogonal directions in-plane: (i) the direction defined by the axis along two nearest-neighbor N atoms (which we refer to below as the N direction) and (ii) the direction along the axis defined by two nearest-neighbor hollow sites (the hollow direction). As seen in the cross sections, the N atoms are slightly above the plane of the surface Cu atoms. In addition, there is a net transfer of charge from the Cu atoms to the N atoms (*25*). A comparison of the charge densities along the two orientations shows that the CuN has formed a network of polar covalent bonds along the N rows that is distinct from the underlying bulk Cu.

Placing an Fe or Mn atom on top of a Cu atom in the CuN surface causes a substantial rearrangement of the atomic structure. As seen in Fig. 1C for Fe, the Cu atom directly below the magnetic atom has moved toward the bulk and is no longer part of the polar covalent CuN network. The magnetic atom transfers charge to the CuN surface and creates bonds with its neighboring N atoms; the magnetic atom is thus incorporated into the extended molecular network on the surface. In spite of these extensive structural changes, we can reversibly attach and remove both Fe and Mn atoms from the CuN surface with the STM tip using a previously described technique (*15*).

The conductance spectra obtained over two different Fe atoms on different CuN islands at various in-plane magnetic fields are shown in Fig. 2, A and B. At $B = 0$, three clear steps are seen centered at $|V_0| \cong 0.2$, 3.8, and 5.7 mV (*26*). In the framework of inelastic electron tunneling spectroscopy (IETS) (*27*), these steps in conductance are interpreted as the opening of an inelastic tunneling channel associated with the creation of an excitation at energy eV_0, where e is the magnitude of the electron charge and V_0 is the center of the step. Changes in energy and intensity of these excitations as a function of B allow us to assign them to spin excitations (*14*, *15*). For a single orientation of B, the atoms were placed at different Cu sites on the surface so that the field was oriented along two different spatial directions: the N direction (for the atom in Fig. 2A) and the hollow direction (Fig. 2B). The existence of zero-field excitations indicates that the different spin orientations (quantum number m) are nondegenerate even in the absence of a magnetic field, suggesting the presence of strong magnetic anisotropy in the system even for a single atomic spin on the CuN surface. Surprisingly large magnetic anisotropies have also been observed for isolated metal atoms on bare metal surfaces (*1*).

In Fig. 2, C and D, the evolution of the energies of the IETS steps seen in Fig. 2, A and B, is shown. The changes in the excitation energies are markedly different when the magnetic field is applied in the two different directions: When B is along the N direction (Fig. 2C), all of the step energies increase with B, whereas the first and third steps decrease in energy when B is applied along the hollow direction (Fig. 2D). At a given in-plane magnetic field, it was possible to move an individual Fe atom back and forth between the two distinct binding sites (i.e., sites so that B was oriented along either the N or hollow direction) and observe that the excitation spectrum switched correspondingly. These differences can be unambiguously observed only because we can probe individual magnetic atoms in a well-characterized environment. A third distinct behavior is seen when the magnetic field is applied in the out-of-plane direction on a different Fe atom, as illustrated in fig. S1 (*28*); in this case, very little change of the step energies is observed. This strong dependence of the spin excitations on field direction is further evidence of strong magnetic anisotropy for the Fe spin.

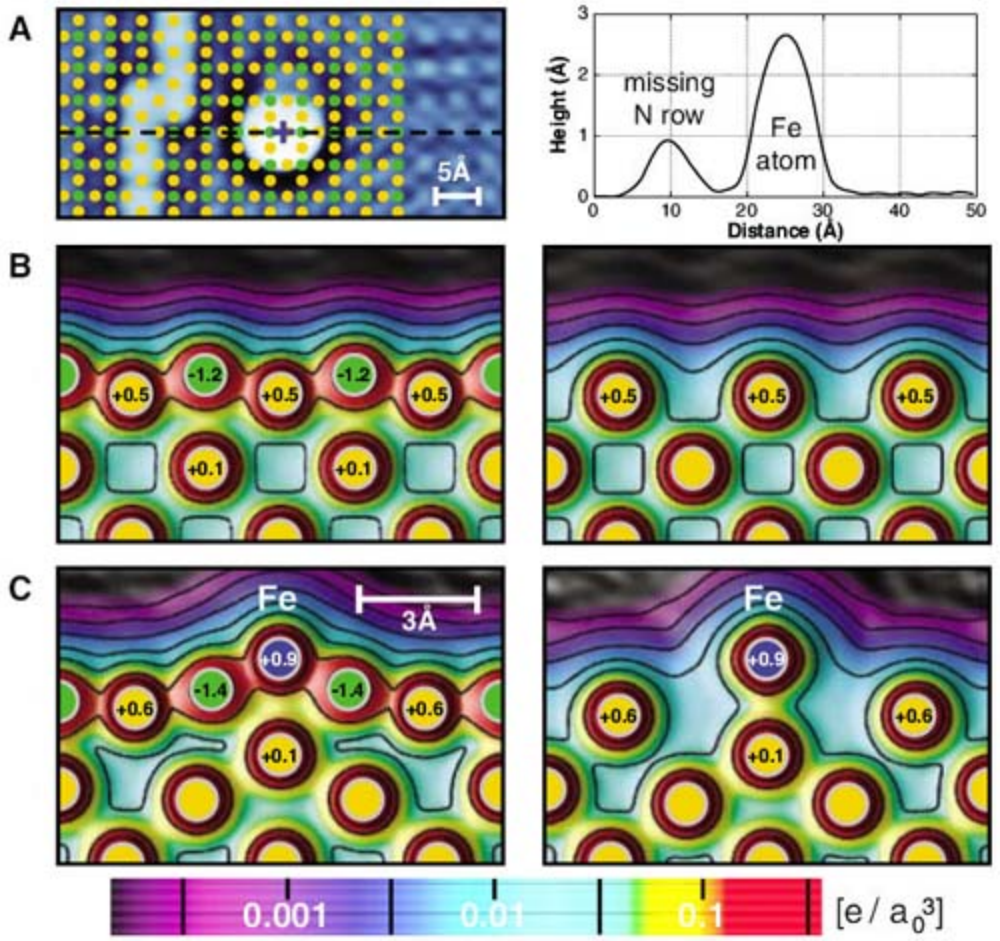

Fig. 1. Fe atoms on CuN. (**A**) (Left) Processed (*37*) constant-current topograph (10 mV, 0.5 nA) of two adjacent CuN islands with a single adsorbed Fe atom. The topograph is negative-curvature (high-pass) filtered to enhance contrast, with lattice positions of Cu (yellow dots) and N (green dots) atoms overlayed. The light vertical features on the left side of the image are formed by the absence of single rows of N atoms from the CuN surface. The topographic peak of the Fe atom (blue cross) shows its binding site: on top of a Cu site with two N atoms as horizontal neighbors. (Right) Cross section of the unfiltered topograph along the dashed line indicated in the left panel. (**B**) The charge density for a CuN surface on Cu(100) calculated with the DFT methods described in the text along the N (left) and hollow (right) directions. The scale for the magnitude of the charge density is shown at the bottom in units of e/a_0^3. Solid yellow and green circles with gray edges label the centers of the Cu and N atoms, respectively. The numbers inside the circles indicate the net charge on selected atoms in units of e (*25*). (**C**) Same as (B) with an Fe atom (blue) adsorbed on the CuN on top of a surface Cu site.

To lowest order, spin excitations in an anisotropic environment can be described by the spin Hamiltonian (*5*)

$$\hat{H} = g\mu_B \vec{B} \cdot \hat{\vec{S}} + D\hat{S}_z^2 + E(\hat{S}_x^2 - \hat{S}_y^2) \quad (1)$$

Here the first term is the Zeeman splitting of the states in the presence of a magnetic field, where g is the g-factor, μ_B is the Bohr magneton, and $\hat{\vec{S}} = (\hat{S}_x, \hat{S}_y, \hat{S}_z)$ is the spin operator. The second and third terms are phenomenological representations of the axial and transverse magnetic anisotropies, characterized by strengths D and E, respectively. The axial term splits the degeneracy of the spin-states on the basis of the magnitude of the spin's z projection m, whereas the transverse term mixes states of different m. By convention, the axes are assigned in Eq. 1 to maximize $|D|$ and have $E > 0$.

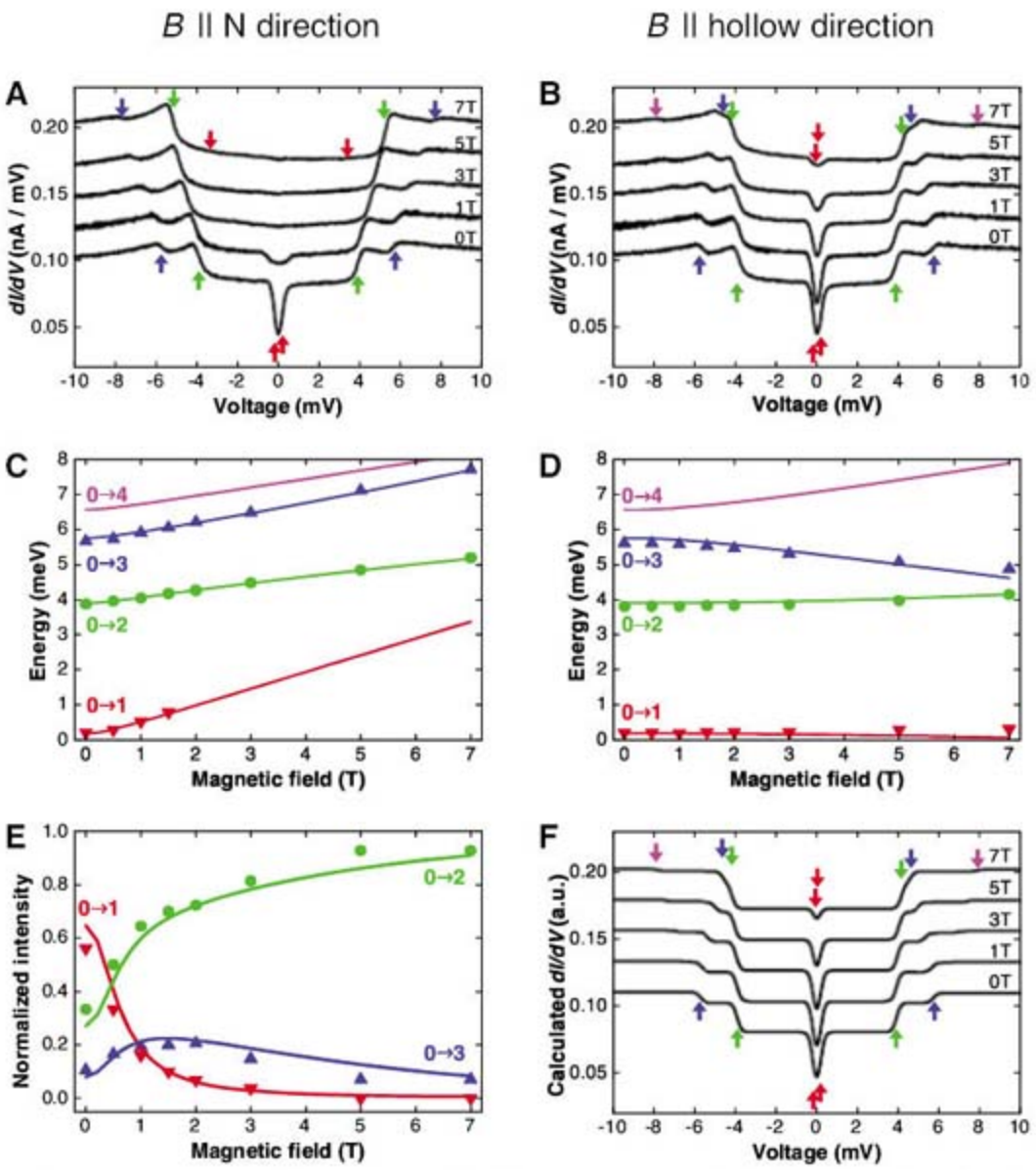

Fig. 2. Conductance spectra of Fe atoms on CuN. (**A**) Spectra taken with the STM tip positioned above an Fe atom at $T = 0.5$ K and $B = 0$ to 7 T oriented in the N direction. The spectra were acquired at a nominal junction impedance of 10 megohm (10 mV, 1 nA) and were not sensitive to junction impedance. Successive spectra are vertically offset by 0.023 nA/mV for clarity. Red, green, and blue upward arrows indicate the positions of the first, second, and third excitations, respectively, at $B = 0$ T as calculated by Eq. 1 with the fit parameters described in the text. Downward arrows show the same excitations at $B = 7$ T with the magnetic field oriented along the z axis of Eq. 1. (**B**) Same as (A) with B oriented along the hollow direction for the spectra; this direction corresponds to the x axis of Eq. 1. Also included are magenta downward arrows indicating the calculated position of the fourth transition at $B = 7$ T. (**C**) Energies for the first (red triangles), second (green circles), and third (blue triangles) steps observed in the spectra acquired with B along the N direction, including those shown in (A). Solid lines indicate excitation energies calculated by Eq. 1 with the magnetic field oriented along the z axis. (**D**) Step energies for the spectra acquired with B along the hollow direction, which corresponds to the x axis of Eq. 1, including those shown in (B). (**E**) Relative step heights for the first (red), second (green), and third (blue) excitations as a function of B along the N direction. The individual step heights are normalized by the sum of the three step heights at each value of B. The fourth excitation is not included because its intensities are negligible in this range of B. Solid lines denote normalized transition intensities calculated using Eq. 2 with the fit parameters discussed in the text. (**F**) Simulated spectra, as described in the text, with B along the hollow direction and an effective temperature of 0.8 K. Arrows are the same as in (B). These spectra are scaled by an overall constant and offset to match those shown in (B). a.u., arbitrary units.

Diagonalization of Eq. 1 allows us to calculate the excitation spectrum for the spin system. Using the spin of a free Fe atom ($S = 2$) (*29*), a best fit of all of the excitations shown in Fig. 2, C and D, and fig. S1B (*28*) yields $g = 2.11 \pm 0.05$, $D = -1.55 \pm 0.01$ meV, and $E = 0.31 \pm 0.01$ meV; here the uncertainties are the standard errors produced by the best fit. $D < 0$ favors high $|m|$ states, which are desirable for achieving magnetic bistability with a long lifetime (*4*). However, the relatively large transverse E term mixes the different spins states, making these structures unsuitable for use as bistable spin systems. It may be possible to remove such mixing by engineering the local environment of the atomic spin, for example, by positioning the magnetic atom on a surface site with higher symmetry. Similar magnetic-anisotropy values, although usually with positive D (corresponding to planar or hard-axis anisotropy), have been observed in studies of crystals formed from molecular magnet structures with single Fe atoms (*30*).

Figure 2, C and D, and fig. S1B (*28*) show the agreement between the observed IETS step energies and the excitation energies calculated from Eq. 1 as a function of B. In these calculations, the direction of B along the N, hollow, and out-of-plane directions is associated with the z, x, and y axes in Eq. 1, respectively. A fourth excitation at a higher energy is also predicted to occur. Although no indication of this excitation is observed for B along the N and out-of-plane directions, a weak conductance step at the predicted energies is observed at larger magnetic fields applied along the hollow direction, as seen in Fig. 2B. Unexpectedly, the primary anisotropy axis (corresponding to the z axis in Eq. 1) is not directed out-of-plane but rather along the in-plane N direction (i.e., along the direction of the CuN molecular network). This result indicates the importance of the local molecular-bonding environment in determining the magnetocrystalline anisotropy.

To better understand the inelastic tunneling process that governs the spin excitations observed with IETS, we also analyzed the intensity of the transitions as a function of magnetic-field strength and orientation. In Fig. 2E, the relative intensities of the three strong IETS steps as a function of B along the N direction are shown. We found that the relative IETS step heights for transitions between an initial spin eigenstate ψ_i and a final spin eigenstate ψ_f are well-described by

$$I_{i\to f} = \left|\langle\psi_f|\hat{S}_x|\psi_i\rangle\right|^2 + \left|\langle\psi_f|\hat{S}_y|\psi_i\rangle\right|^2 + \left|\langle\psi_f|\hat{S}_z|\psi_i\rangle\right|^2 = \tfrac{1}{2}\left[\left|\langle\psi_f|\hat{S}_+|\psi_i\rangle\right|^2 + \left|\langle\psi_f|\hat{S}_-|\psi_i\rangle\right|^2 + 2\left|\langle\psi_f|\hat{S}_z|\psi_i\rangle\right|^2\right] \quad (2)$$

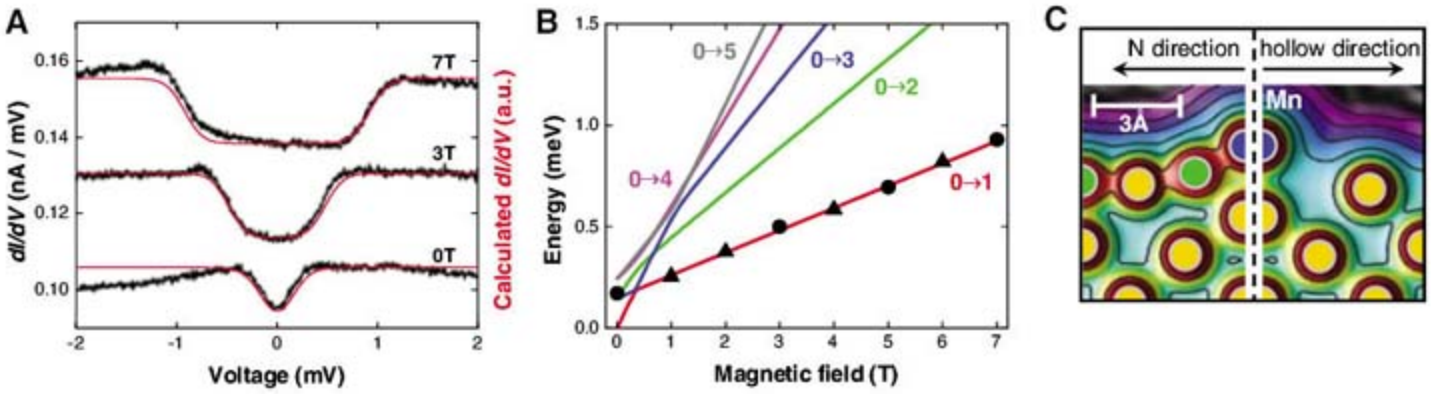

Fig. 3. Conductance spectra and structure of Mn atoms on CuN. (**A**) Spectra (black) taken with the tip positioned above a Mn atom at T = 0.5 K, with the magnetic field oriented out-of-plane. All spectra were acquired at a nominal junction impedance of 10 megohm (10 mV, 1 nA) and are offset by 0.025 nA/mV for clarity. Red lines represent simulated spectra with an effective temperature of 0.7 K. The simulated inelastic spectra are scaled by an overall constant and offset to match the observed spectra. (**B**) Step energy of two different Mn atoms, indicated by circles and triangles, with B oriented out-of-plane. Colored lines show the possible transitions energies calculated using Eq. 1 with the fit parameters listed in the text for B along the z direction. Because the anisotropy parameters are substantially smaller than those for Fe, level crossings complicate the assignment of the spin excitations at small magnetic fields. (**C**) Charge density for a Mn atom adsorbed on a CuN surface on Cu(100) calculated by DFT along the N and hollow directions. Solid yellow, green, and blue circles with gray edges label the centers of the Cu, N, and Mn atoms, respectively. The charge-density scale is the same as that shown in Fig. 1.

Table 1. Eigenvectors of the spin Hamiltonian for Fe on CuN. A list of eigenvectors, written as a sum of $|m\rangle$ states and obtained by diagonalizing Eq. 1 with $S = 2$, $g = 2.11$, $D = -1.55$ meV, and $E = 0.31$ meV at B = 0 T and at B = 7 T oriented along the N direction is shown.

Eigenstate	$\|+2\rangle$	$\|+1\rangle$	$\|+0\rangle$	$\|-1\rangle$	$\|-2\rangle$
			$B = 0$ T		
ψ_0	0.697	0	−0.166	0	0.697
ψ_1	0.707	0	0	0	−0.707
ψ_2	0	0.707	0	−0.707	0
ψ_3	0	0.707	0	0.707	0
ψ_4	0.117	0	0.986	0	0.117
			$B = 7$ T		
ψ_0	0.021	0	−0.097	0	0.995
ψ_1	0.987	0	−0.157	0	−0.036
ψ_2	0	0.402	0	−0.916	0
ψ_3	0	0.916	0	0.402	0
ψ_4	0.159	0	0.983	0	0.092

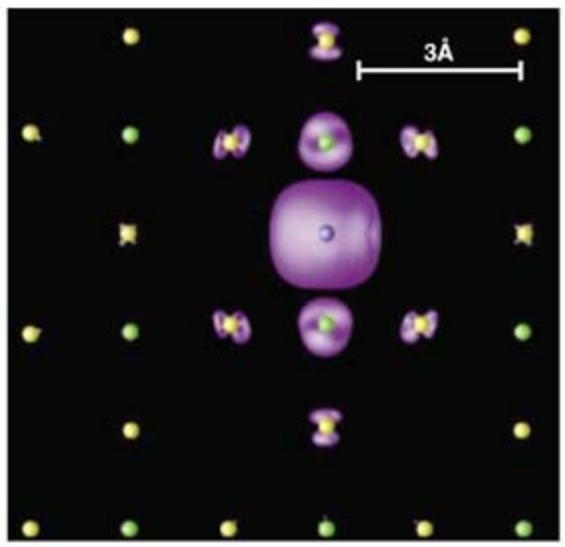

Fig. 4. Calculated net–spin-density distribution for Fe on CuN. Contours (purple) of constant net spin density (0.01 e/a_0^3), as calculated by DFT for an Fe atom adsorbed on a Cu site on a CuN surface, are shown (*25*). Only the Fe atom and the atoms in the CuN surface layer are shown for clarity. Small yellow, green, and blue balls indicate the positions of the Cu, N, and Fe atoms, respectively, in the surface layer.

where $\hat{S}_{\pm} = \hat{S}_x \pm i\hat{S}_y$ (here, $i = \sqrt{-1}$) and ψ_i and ψ_f are obtained directly from the diagonalization of Eq. 1. As shown in Table 1, ψ_0 has most of its weight in the $|m = +2\rangle$ and $|-2\rangle$ states when B = 0 T. This makes $\Delta m = 0$ transitions (where Δm is the change in m) to the ψ_1 state and $\Delta m = \pm 1$ transitions to the ψ_2 and ψ_3 states strong, whereas transitions to the ψ_4 state are forbidden. At B = 7 T along the N direction (see Table 1), the situation changes substantially: Because most of the weight in ψ_0 is now in the $|-2\rangle$ state, $\Delta m = \pm 1$ transitions to the ψ_2 and ψ_3 states remain visible, whereas $\Delta m = 0$ transitions to the ψ_1 and ψ_4 states are too weak to observe. The $\Delta m = 0, \pm 1$ requirement implied by Eq. 2 is consistent with previous empirically observed selection rules in STM spin-excitation experiments (*15*).

The spin-transition matrix element described in Eq. 2 is the same as the matrix element for inelastic neutron scattering in a polycrystalline magnetic system (*31*). We suggest that the observed inelastic tunneling arises from similar magnetic interactions between the spin of the tunneling electron and the spin of the magnetic atom—either direct dipolar interactions or through an exchange interaction. The intensity of this inelastic process is remarkably large for a single Fe atom on CuN: At B = 0, the inelastic conductance (i.e., the sum of the IETS steps) is at least as large as the elastic conductance (as measured at V = 0). Resonant enhancement of the inelastic tunneling resulting from a coincidence of the relevant orbitals may explain its relative prominence.

We can model the full conductance spectra as the sum of (i) a voltage-independent elastic conductance and (ii) a series of thermally broadened IETS transitions (*27*) weighted by the transition intensities given in Eq. 2 and by the Boltzmann population of the filled initial and empty final states. A comparison of Fig. 2, B and F, demonstrates the excellent agreement between the measured and calculated spectra. Similar agreement is also seen when B is oriented in the other directions discussed above [fig. S1C in (*28*)].

Substantially weaker magnetic anisotropy is observed for Mn atoms on CuN, even though its local chemical environment is very similar to that of Fe. Figure 3A shows IETS spectra obtained for Mn on CuN, with B oriented out-of-plane; spectra obtained in the two in-plane directions are also shown in fig. S2A (*28*). Using the spin of a free Mn atom ($S = \frac{5}{2}$) (*15*), a best fit of the excitation energies from two different Mn atoms on two different CuN islands (Fig. 2B) to Eq. 1 yields $g = 1.90 \pm 0.01$, $D = -0.039 \pm 0.001$ meV, and $E = 0.007 \pm 0.001$ meV. As seen in Fig. 3 and fig. S2 (*28*), agreement between the calculated and observed transition energies and the spectral line shapes is excellent for different Mn atoms in all three orientations of B. In contrast to the results for Fe, however, these results indicate that the easy axis (z axis in Eq. 1) for Mn is oriented out-of-plane. A comparison of the DFT calculations of the structures for Fe and Mn on CuN (Figs. 1C and 3C, respectively) shows that they are similar and does not suggest an obvious reason for the change in orientation of the anisotropy axis. The small size of D is

consistent with anisotropy values observed for Mn in molecular magnetic clusters (*30*).

For both Fe and Mn on CuN, we find that the excitation spectrum is well described by a net spin identical to the free-atom spin (i.e., S = 2 for Fe and $^5/_2$ for Mn). For comparison, we performed spin-resolved DFT calculations for these systems and found that most of the net spin is localized on the magnetic atom and the surrounding interstitial region (*25*): S = 1.73 for Fe and 2.28 for Mn. However, a substantial amount of spin density extends into the surrounding atoms, as illustrated in Fig. 4 for Fe, where we find that the spin spreading occurs primarily along the N direction in the surface molecular network. By including the spin of all of the atoms, the net spin of the total structure is calculated to be the same as that of the free magnetic atoms: S = 2.00 for Fe and 2.50 for Mn. In comparison, no substantial net spin density is found for bare CuN on Cu(100). This spreading of spin density, here up to 4 Å from the Fe binding site, is similar to that reported in DFT calculations of molecular magnets (*32*). Further analysis of the qualitative differences in the spatial distribution of the net spin for the case of Mn and Fe may yield insight into the atomic-scale origins of the differences in their observed anisotropies.

The surface-embedded molecular magnetic structures we have described here are model systems for the study of magnetic anisotropy on surfaces. These structures are similar to molecular magnets because the individual magnetic atoms are incorporated into a molecular-bonding network. In contrast to molecular magnets, the structures studied here can be constructed, probed, and manipulated atom-by-atom. The results presented here provide a detailed phenomenological picture of the magnetic anisotropy for a single atomic spin in a well-characterized environment. Further theoretical and experimental studies of these systems may allow for the development of a fully microscopic picture of the atomic-scale origins of magnetocrystalline anisotropy. Combining this with the ability to couple atomic spins into extended quantum-spin structures may eventually enable the development of systems in which giant magnetic anisotropy can be completely engineered at the atomic scale.

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25. From the calculated electronic states of the optimized structure, we obtained the charge on each atom by a Bader analysis (*35*). We determined the spin by separately calculating the total number of electrons with spin up $N_\uparrow$ and spin down $N_\downarrow$ in a specified volume and then subtracted them to yield $S = (N_\uparrow - N_\downarrow)/2$.
26. These excitation energies changed by less than ±5% for Fe atoms adsorbed on different CuN islands and measured with different tips. This variation may arise from slight changes in the local environment caused by the inherent strain in the CuN islands (*36*).
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Supporting Online Material

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Figs. S1 and S2

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Current-Induced Hydrogen Tautomerization and Conductance Switching of Naphthalocyanine Molecules

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The bistability in the position of the two hydrogen atoms in the inner cavity of single free-base naphthalocyanine molecules constitutes a two-level system that was manipulated and probed by low-temperature scanning tunneling microscopy. When adsorbed on an ultrathin insulating film, the molecules can be switched in a controlled fashion between the two states by excitation induced by the inelastic tunneling current. The tautomerization reaction can be probed by resonant tunneling through the molecule and is expressed as considerable changes in the conductivity of the molecule. We also demonstrated a coupling of the switching process so that the charge injection in one molecule induced tautomerization in an adjacent molecule.

The concept of using single molecules as electronic components is well-established, with many examples on small numbers of or even individual molecules serving as memory elements, diodes, transistors, or switches (*1*–*5*). However, to construct more complex molecular devices requires that components are brought together and electronically coupled in a controlled manner. Most molecular switches are based on drastic conformational changes in the molecule (*6*–*9*); this is not compatible with the aim of controlling the coupling between the mol-

ecules. The development of molecular logic devices will also require single-molecule switches that can be coupled without compromising their function and that do not involve changes in the molecular frame.

Here, we present a single-molecule switch based on hydrogen tautomerization that meets these requirements. We operated and characterized the switch by low-temperature scanning tunneling microscopy (STM). The lowest unoccupied molecular orbital (LUMO) of a free-base naphthalocyanine (Fig. 1B) can have two orientations, depending on the position of the two inner hydrogens in the central cavity of the molecule (arrow in Fig. 1B). By increasing the bias voltage between the tip and the sample, a hydrogen tautomerization reaction can be induced by the tunneling electrons in the scanning tunneling microscope junction. This change is formally equivalent to the rotation of the molecule by 90° and causes a substantial change in the tunneling current measured at the scanning tunneling microscope tip positioned over the molecule. Because the switching is well-defined, highly localized, reversible, intrinsic to the molecule, and does not involve changes in the molecular frame, this class of molecules can be used as building blocks for more complex molecular devices such as logic gates.

The molecules were adsorbed on ultrathin insulating films (NaCl, RbI, and Xe) on Cu single crystals and studied by low-temperature STM operated at $T = 5$ K (*10*–*13*). Individual naphthalocyanine molecules were adsorbed at a sample temperature of $T = 5$ K, with the sample located in the scanning tunneling microscope. Bias voltages refer to the sample voltage with respect to the tip.

A tunneling spectrum (with current I and differential conductance dI/dV as a function of the bias voltage V) acquired on an isolated naphthalocyanine molecule on a NaCl(100) bilayer on Cu(111) (Fig. 1A) shows two resonances corresponding to the tunneling through the LUMO and highest occupied molecular orbital (HOMO) at a positive and negative bias, respectively. The molecule is adsorbed along the nonpolar [100] direction of the substrate; this is the most stable configuration on NaCl and RbI insulating films. The corresponding STM images acquired with a molecule-terminated tip at bias voltages corresponding to the resonances and to in-gap conditions are shown in Fig. 1B. As shown previously (*12*), the unperturbed molecular orbitals can be directly imaged by STM, and they compare very well with the calculated electronic wave-functions of a free molecule. The computed orbitals shown in Fig. 1 are based on density functional theory (DFT) calculations at the B3LYP/TZV level (*14*). The LUMO image allows for easy determination of the position of the inner hydrogens: They impose D_{2h} symmetry on the molecule, which is reflected in the LUMO over the entire molecule. The "arms" with hydrogens show a single-lobe structure at the end, as opposed to the nodal plane along the other two arms.

The energy resolution in tunneling spectra can be increased by changing the insulating film to RbI (*13*), and we can resolve the peaks corresponding to the LUMO and LUMO+1 orbitals in the spectrum shown in Fig. 1C. These orbitals are separated by ~0.23 eV and cannot be resolved separately in the dI/dV spectra on NaCl films. The difference in the energy of the LUMO resonance as compared with the measurements on NaCl is caused by the different work functions of the substrates (*12*). Constant-height dI/dV images acquired with a metallic tip (Fig. 1D) illustrate how the LUMO and LUMO+1 have the same nodal structure but are rotated by 90° with respect to each other. These experiments are again well corroborated by DFT calculations of the free molecule concerning both the orbital structure and the energy separation between the LUMO and LUMO+1 (0.19 eV). The separation of the LUMO and LUMO+1 images in the experiment is important for the direct assignment of the two different electronic states with the two different tautomers.

The hydrogen tautomerization can be induced by positioning the tip above the molecule and substantially increasing the bias above the LUMO resonance. Because the LUMO images are distinctly different for the two tautomers, the reaction can be directly monitored in the current signal or vertical-tip position in constant-height or constant-current mode, respectively. In these measurements, the current or vertical-tip position switches back and forth between two well-defined levels, as shown in Fig. 2A for a bias voltage of 1.7 V. When we lower the bias and image the LUMO at resonance, the two current levels correspond to a 90° rotation of the orientation of the LUMO. On the basis of the DFT calculations and optical and NMR spectroscopy (*15*), this observation can be assigned to changes in the position of the imino hydrogens in the central cavity; i.e., hydrogen tautomerization (Fig. 2B). A rotation of the whole molecule can be ruled out as we observe the switching of molecules at step edges and in arrays of molecules, where a rotation of the molecule cannot occur. In addition, we also observe switching on a Xe monolayer, where a rotation of the molecule by 90° would be incompatible with the symmetry of the surface.

The dependence of the switching rate on the current is linear, and the distribution of residence times in the low- and high-current states is exponential. These observations are consistent with a statistically independent one-electron process. The switching rate increases with increasing bias voltage in a roughly exponential fashion (Fig. 2C, measurements in constant-current mode). Because no saturation is observed in the experimentally accessible range of

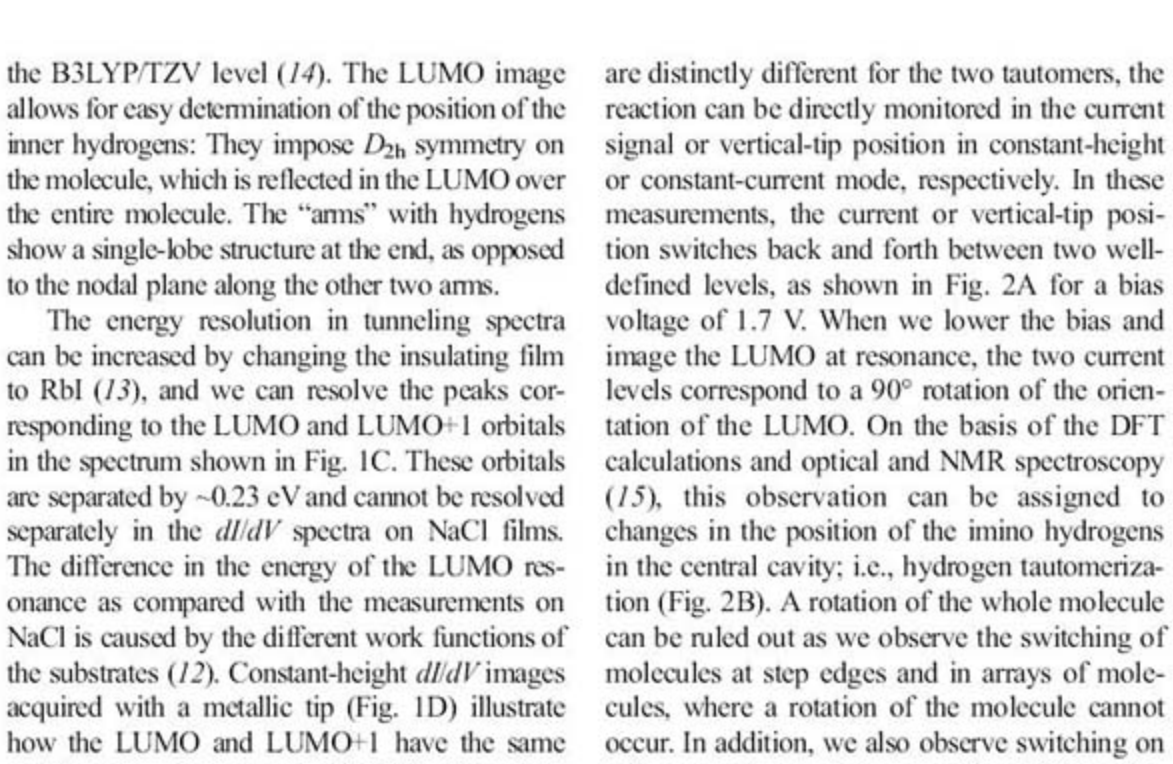

Fig. 1. Spectroscopy and orbital images of naphthalocyanine obtained by low-temperature STM operated at $T = 5$ K. (**A**) Spectroscopy of naphthalocyanine on a NaCl bilayer on Cu(111) where the peaks correspond to tunneling into the LUMO (positive bias) and out of the HOMO (negative bias). (**B**) STM images at 1 pA, −1.6 V (left) and 1 pA, 0.65 V (right), as well as at low bias (1 pA, 0.05 V) compared with the calculated HOMO and LUMO of the free molecule. The lower center panel shows the structure model to scale where the arrow indicates the central hydrogen atoms that are along the horizontal arms. The STM images were obtained with a molecule-terminated tip. (**C**) Spectroscopy of naphthalocyanine on a RbI bilayer can resolve both the LUMO and the LUMO+1 (separated by ~0.23 V). a.u., arbitrary units. (**D**) Corresponding orbital maps to (C); in this case, the dI/dV signal is in the constant-height mode, as compared with DFT calculations. All images are 30 by 30 Å^2.

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resolvable switching rates, we think that the resonance responsible for the switching is at an even higher voltage (*16*). At voltages corresponding to the LUMO resonance (switch readout), switching was not observed. There is a slight but significant deviation from purely exponential dependence that may help to reveal the details of the switching process in conjunction with future theoretical efforts.

There is a strong dependence of the switching rate on the position of the electron injection into the molecule (Fig. 2D). Each pixel in Fig. 2D corresponds to a time trace with 100 switching events on average, giving in total ~75,000 switching events over the molecule. The spatial map corresponding to the reverse reaction is similar but rotated by 90°. The white pixels in Fig. 2D at the center of the molecule do not indicate a zero switching rate; instead they signify that we cannot observe the tautomerization reaction in the time traces, because both tautomers result in the same current for symmetry reasons. These measurements were carried out in constant-current mode, and thus the switching rate is directly proportional to the quantum yield of the process. Figure 2D also shows that the switching probability is distinctly different on the two inequivalent arms of the molecule. This difference can be exploited to control the direction of the tautomerization reaction: If the current is injected in a position where the probabilities for switching back and forth are very different, the final position of the hydrogen atoms can be selected with a high probability (~90%). However, the striking feature apparent in these plots is that the largest switching rate is achieved when the tip is above the far periphery of the molecule (i.e., >10 Å from the reaction site). This is in contrast with the typical inelastic electron-tunneling mechanism if no insulating film is present (*17*–*21*). Because of decoupling provided by the insulating film, the lifetime of an additional electron in a molecular resonance is expected to be relatively long (*13*, *16*, *22*). To study this effect in more detail, we spatially mapped the switching rate on one, two, and three monolayers of RbI. On one RbI monolayer (shortest lifetime), the highest switching rate was achieved near the center of the molecule. On two and three monolayers of RbI, we observed similar spatial dependence, as shown in Fig. 2D. When the molecules were directly adsorbed on a Cu(100) substrate, we could not observe tautomerization.

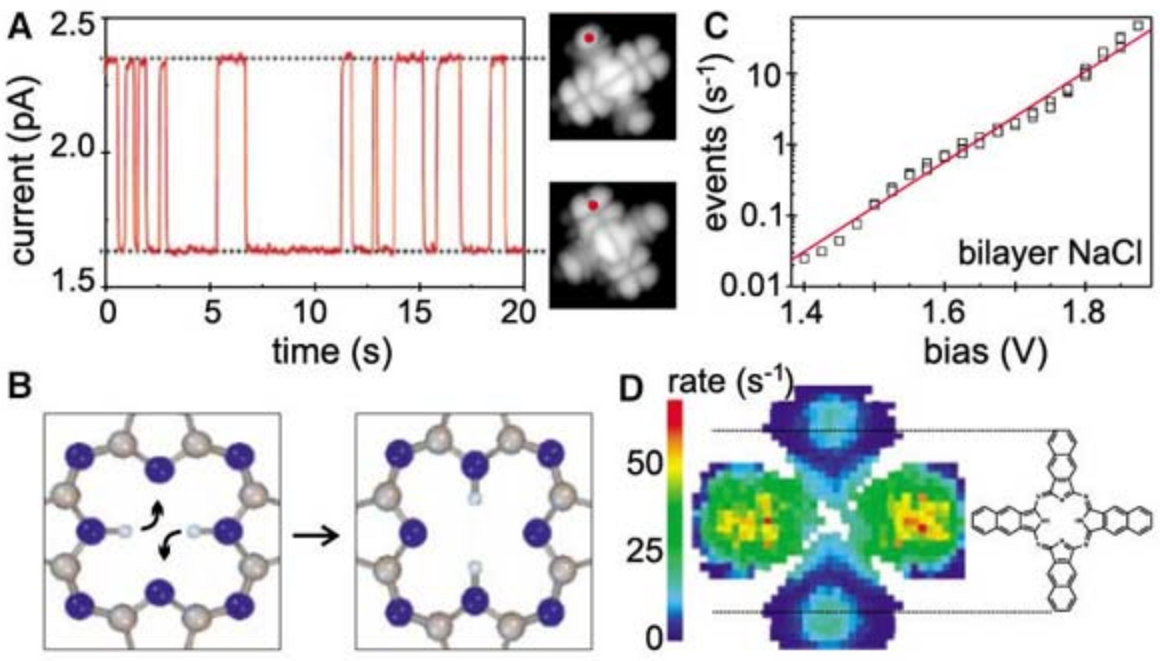

Fig. 2. Switching of a single naphthalocyanine molecule by the tunneling current. (**A**) (Left) Current-trace obtained at a bias of 1.7 V when the tip was positioned at one end of the molecule (red dot in STM images). (Right) Orbital images showing the orientation of the LUMO corresponding to the high- or low-current state (2 pA, 0.7 V). (**B**) Schematic of the hydrogen tautomerization reaction responsible for the switching. (**C**) The bias dependence of the switching rate measured with a tunneling current of 1 pA on a naphthalocyanine molecule on a NaCl bilayer on Cu(111), showing an overall exponential trend with a slope of 165 mV/decade. (**D**) Spatial map of the switching rate for the hydrogen tautomerization reaction shown in (B) for a tunneling current of 1 pA at a bias of 1.825 V. For reference, the structure of the molecule is displayed to scale.

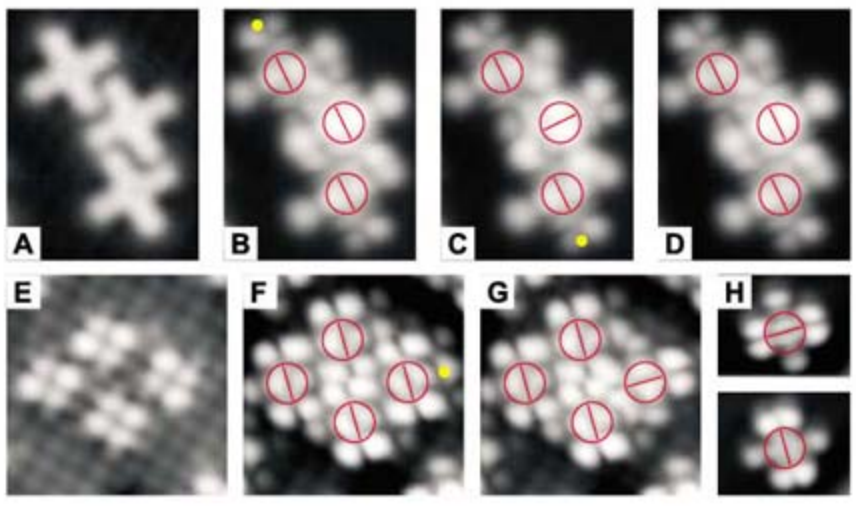

Fig. 3. Examples of interacting and noninteracting assemblies of molecular switches. (**A**) A trimer of naphthalocyanine molecules on a NaCl bilayer formed by STM manipulation (image obtained at 2 pA, 0.3 V). (**B** to **D**) Current injection through the top or bottom molecules of the trimer [yellow dots in (B) and (C)] can cause the switching of the molecule in the middle, as shown by the LUMO images (2 pA, 0.8V). Images are 44 by 58 Å^2. (**E**) Arrays of phthalocyanine molecules on a RbI monolayer on Cu(331). The in-gap image shows four phthalocyanine molecules that were isolated from a larger array of molecules (1 pA, −0.1 V). (**F**) Image at a bias voltage corresponding to the LUMO (1 pA, −0.5 V) (*24*). Current injection through the point indicated by a yellow dot induces only the switching of the molecule directly under the scanning tunneling microscope tip, as shown in the LUMO images in (**G**). Images in (E) to (G) are 50 by 50 Å^2. (**H**) The two orientations of the LUMO of an isolated phthalocyanine molecule (2 pA, 0.35 V).

The spatial dependence of the switching probability highlights the role of electron and/or energy transport within the molecule, making this system particularly interesting for related studies. For example, we can probe the coupling between neighboring naphthalocyanine molecules. We have coupled together three naphthalocyanines by simply bringing them close together by STM lateral manipulation (*23*), as shown in Fig. 3, A to D. In this configuration, we can switch one molecule by current injection through the neighboring ones. The switching yield in this experiment is determined by (i) the electron-transport properties through the molecule into which the current is injected, (ii) the coupling of the two adjacent molecules, and finally, (iii) the sensing molecule. Because energy transport in the absence of electron transport between the molecules seems extremely unlikely (by a dipolar or other mechanism), step (ii) corresponds to electron tunneling between the molecules. In this experiment, the molecules are weakly coupled, implying electron tunneling between the molecules but no substantial energy-level hybridization.

We can decrease the coupling of adjacent molecules, as shown for an array of phthalocyanine molecules with a center-to-center distance of 16 Å (Fig. 3, E to H) (*24*, *25*). In this case, the switching of molecules through neighboring ones was not observed, even though the total distance between the injection point (tip) and the reaction site was smaller than in the previous experiment. This finding rules out a field-induced mechanism for the switching.

Switching phenomena within individual molecules could potentially be used as nonvolatile memory with extremely high density, as has been proposed many times (*5*, *6*, *16*, *26*). In contrast to previously investigated systems, the present molecular switch is planar, does not involve confor-

mational changes at the periphery of the molecule, and is well-suited for use in self-assembled monolayers. Another advantage is that the symmetry inherent to the system implies that both positions of the switch have the same total energy and do not differ in binding to the substrate. Thus, we could observe this switching process, on a variety of insulating films (NaCl, RbI, and Xe), for two related molecules (phthalocyanine and naphthalocyanine) and for different charge states of the molecules. These measurements demonstrate the robustness of the process, and given that no changes occur in the molecular framework, it can be anticipated that the switching will also work with molecules embedded in all solid-state devices and in multicore porphyrin-class molecules acting as more complex devices.

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Fig. S1

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Coupled Ferric Oxides and Sulfates on the Martian Surface

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The Mars Exploration Rover (MER), Opportunity, showed that layered sulfate deposits in Meridiani Planum formed during a period of rising acidic ground water. Crystalline hematite spherules formed in the deposits as a consequence of aqueous alteration and were concentrated on the surface as a lag deposit as wind eroded the softer sulfate rocks. On the basis of Mars Express Observatoire pour la Minéralogie, l'Eau, les Glaces et l'Activité (OMEGA) orbital data, we demonstrate that crystalline hematite deposits are associated with layered sulfates in other areas on Mars, implying that Meridiani-like ground water systems were indeed widespread and representative of an extensive acid sulfate aqueous system.

In association with sulfate deposits discovered and mapped inside Valles Marineris, Terra Meridiani, and Margaritifer Terra, ferric oxides have been identified with OMEGA/Mars Express through distinct spectral signatures. These oxides occur in close association with sulfate-rich layered deposits and in low-albedo sand at the base of the deposits. The ferric oxides may thus have formed contemporaneously with sulfate deposits or subsequently (e.g., by diagenetic processes). In either case, the spectral and spatial similarities imply that the formation pathways for sulfate and ferric oxide could have been the same in Valles Marineris and Terra Meridiani, and they likely mimic the geological settings seen on the ground by the MER Opportunity in Meridiani Planum (*1*).

OMEGA, the imaging spectrometer onboard the Mars Express orbiter, acquires spectra in the visible and near infrared wavelength range (0.35 to 5.1 μm) with the use of three different detectors (0.35 to 1.0 μm, 0.95 to 2.6 μm, and 2.5 to 5.1 μm). Its spectral sampling ranges from 7 to 20 nm, and its spatial sampling varies from 300 m to 4 km, depending on the position of the spacecraft on its elliptical orbit (*2*). The instrument has now mapped ~90% of the martian surface at the 1.5- to 5-km scale (*3*).

OMEGA spectra from localized regions in Valles Marineris, Terra Meridiani, and Margaritifer Terra are characterized by an absorption edge between 0.4 and ~0.75 μm; a shallow absorption band, visible as a shoulder, between ~0.6 and ~0.75 μm; a reflectivity maximum at ~0.75 μm; an absorption band centered at ~0.9 μm; and a raise in reflectance up to ~1.3 μm (Fig. 1A). These spectral features are diagnostic for the presence of ferric oxides (Fig. 1B) (*4*), where the two absorption bands and absorption edge result from the single-electron transitions of ferric iron (*5*, *6*). Notably, particle size plays an important role in the strength of ferric absorptions. For example, hematite particles with diameters less than ~10 nm do not have a detectable band minimum at ~0.86 μm, whereas particles with a larger diameter have a distinct, very deep band minimum (*6*, *7*). For specular hematite particles, the band minimum is shallow (*8*). In OMEGA spectra of these areas, the depth of the 0.9-μm ferric signatures reaches 50%, which is more than five times as deep as the common ferric signatures associated with martian bright regions (represented in Fig. 1A for comparison). Some spectra show ferric signatures with sulfate hydration features at ~1.9 and ~2.4 μm or ~2.1 and ~2.4 μm.

The spectral features attributed to ferric oxides in the OMEGA spectra are common to many ferric oxides, including hematite (α-Fe_2O_3), goethite [α-$Fe^{3+}O(OH)$], akaganeite [$Fe^{3+}O(OH,Cl)$], schwertmannite [$\sim Fe_8O_8(OH)_6SO_4 \cdot nH_2O$], lepidocrocite [$\gamma$-FeO(OH)], and ferrihydrite [$Fe^{3+}{}_2O_3 \cdot 5/9(H_2O)$] (*4*). The shape of the ferric feature is distorted when mixed with dust or a minor contribution of olivine or pyroxene. Moreover, oxide signatures can change with temperature, although the spectral changes have been documented only for well-crystalline hematite and goethite (*9*, *10*). Spectral signatures can also strongly depend on oxide crystallinity (*4*). Finally, the ~0.9-μm ferric band is located near a detector change in the OMEGA instrument (~1 μm): The signal-to-noise ratio is lower in this wavelength range, and differences in reflectance between the detectors are commonly observed at

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1 μm. Thus, we cannot at present exclude the presence of any of the ferric oxides listed above on the basis of spectral data.

We also considered the presence of ferric sulfate-bearing phases (schwertmannite is one of these). The hydroxysulfate jarosite [(K, Na, H_3O)$Fe_3(SO_4)_2(OH)_6$] was identified in situ by the MER Mossbauer experiment (*11*, *12*). In the near-infrared wavelength range, jarosite is characterized by narrow diagnostic absorptions at ~1.47, ~1.85, and 2.27 μm [i.e., it is a double feature (doublet)], which are not currently detected in OMEGA spectra. Ferric sulfates generally have a symmetric ~0.9-μm absorption band, with a strong decrease in reflectance between 0.7 and

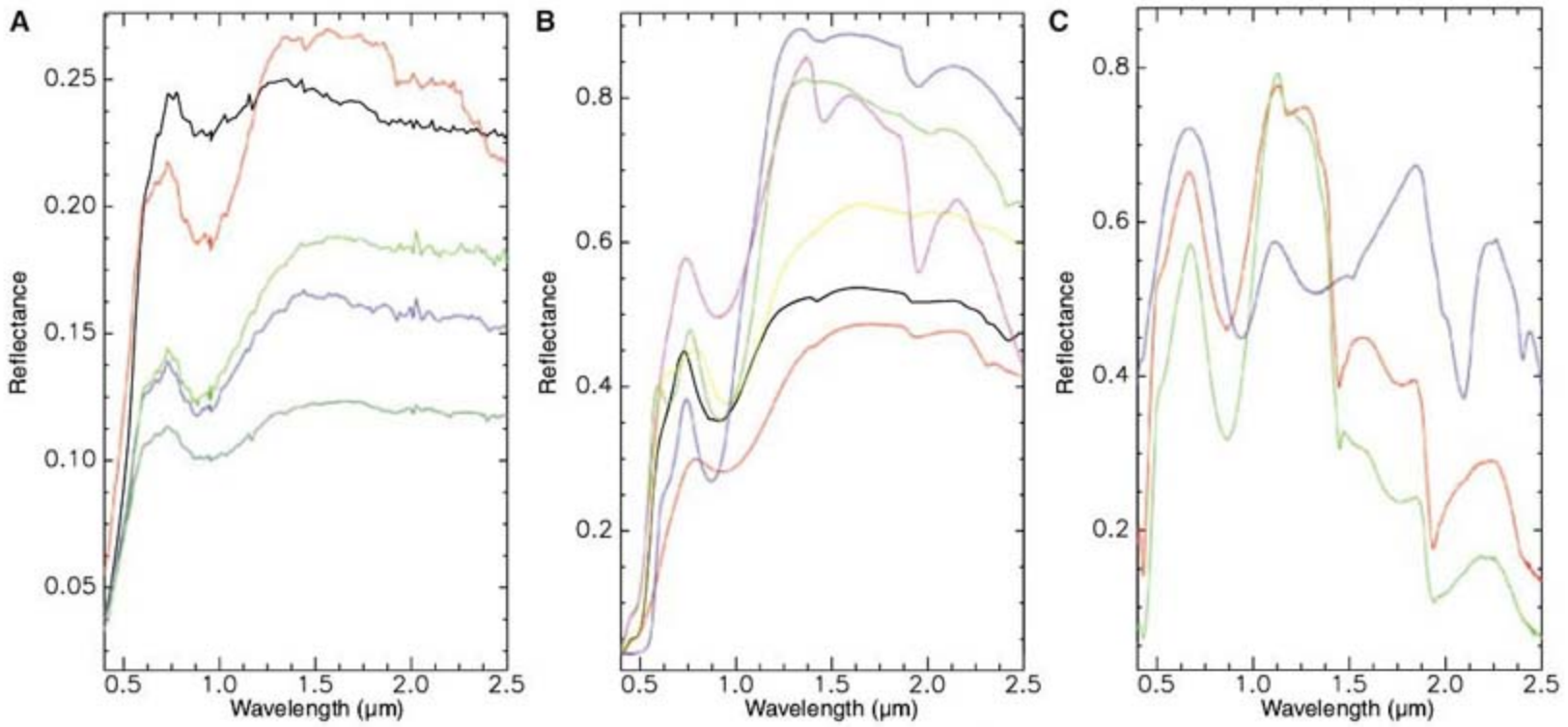

Fig. 1. (**A**) OMEGA spectra of oxide-rich areas, showing Aram Chaos (red), Candor Chasma (light green), Capri Chasma (blue), Meridiani Planum (dark green), and dust for comparison (black). (**B**) Library spectra of the most probable oxides and hydroxides on Mars (*3*) for comparison, including hematite (α-Fe_2O_3) (blue), goethite [α-$Fe^{3+}O(OH)$] (green), lepidocrocite [γ-$FeO(OH)$] (yellow), akaganeite [$Fe^{3+}O(OH,Cl)$] (black), ferrihydrite [$Fe^{3+}{}_2O_3 \cdot 5/9(H_2O)$] (red), and schwertmannite [~$Fe_8O_8(OH)_6SO_4.nH_2O$] (magenta). The hematite mineral has a small component of water in it, whereas the hematite formula does not contain water (Fe_2O_3). (**C**) Library spectra [reproduced from (*9*)] of ferric and ferrous sulfates, including szomolnokite [$Fe^{2+}SO_4 \cdot (H_2O)$] (blue), copiapite [$Fe^{2+}Fe^{3+}{}_4(SO_4)_6(OH)_2 \cdot 20(H_2O)$] (red), and ferricopiapite [$Fe^{3+}{}_{2/3}Fe^{3+}{}_4(SO_4)_6(OH)_2 \cdot 20(H_2O)$] (green).

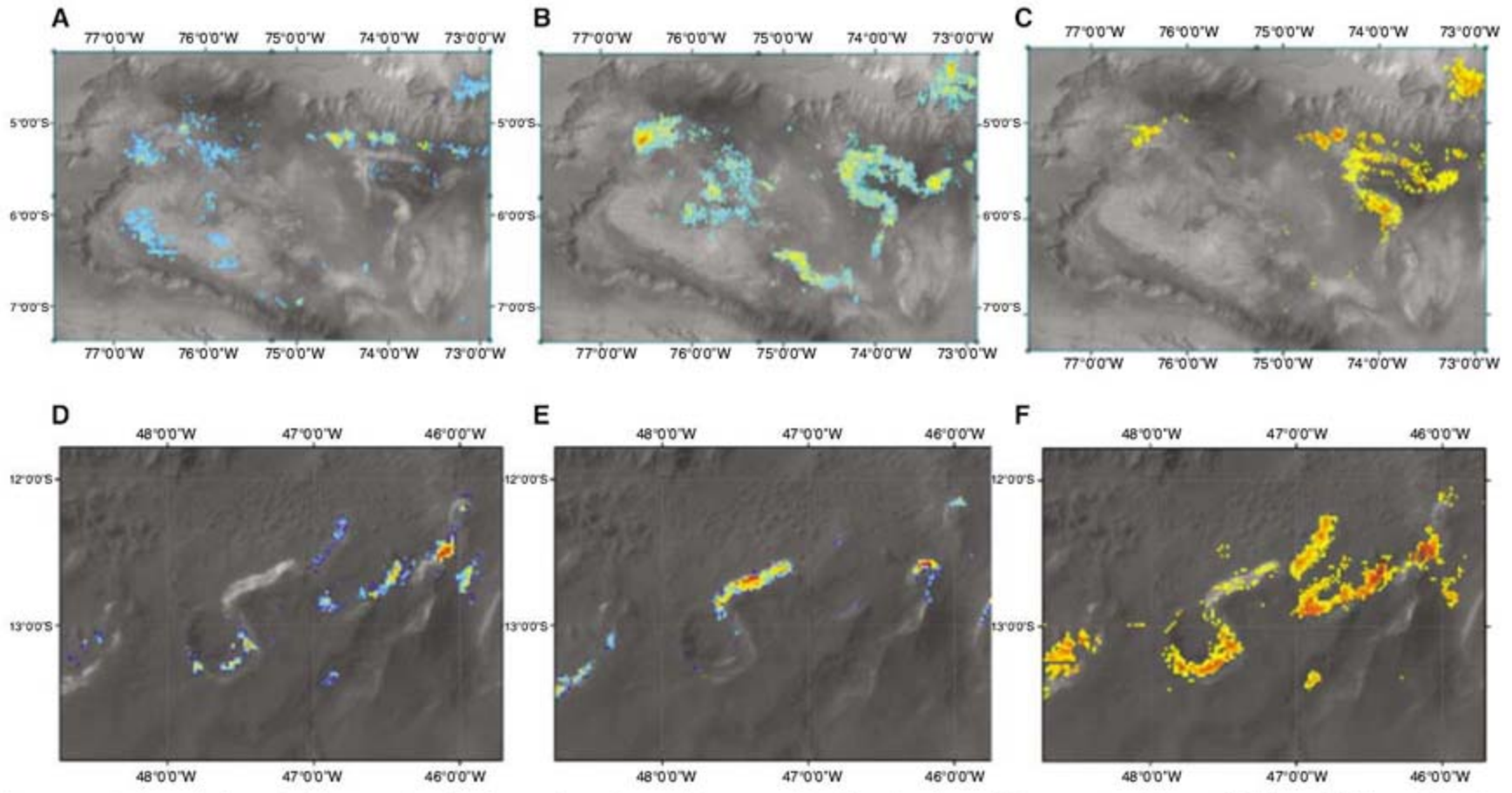

Fig. 2. Spatial association of sulfates and oxides in Candor Chasma [(**A** to **C**), centered at 6°S, 75°W] and Capri Chasma [(**D** to **F**), centered at 13°S, 47°W]. [(A) and (D)] Band depth of 1.9-μm, identified in this case as polyhydrated sulfates (blue = 2%, red ≥ 5%). [(B) and (E)] Band depth of 2.1 μm, identified as kieserite (green = 2%, red ≥ 5%). [(C) and (F)] Oxide band depth, as modeled using the MGM (orange = 10%, red ≥ 30%).

0.9 μm and a strong increase in reflectance between 0.9 and 1.1 μm (*13*), which does not match the very asymmetric OMEGA spectra. Moreover, for similar amplitudes of the 0.9-μm band, the hydration features in the OMEGA spectra—when they are present—are weaker than in ferric sulfate library spectra (Fig. 1C) (*13*). Thus, ferric oxides rather than ferric sulfates constitute the dominant contribution to the spectral signal.

To map the ferric oxides, we used three different methods: the Modified Gaussian Model (MGM) (*14*, *15*), a linear unmixing model (*16*), and the slope between 1.0 and 1.3 μm (using the band ratio between reflectance values at 1.0 and 1.3 μm and selecting the values greater than 15%). The three methods provide concordant results. In Figs. 2 to 4, as well as figs. S1 and S2, we show the results of the MGM-based method. The band depths provided throughout this work represent the strength of the Gaussian corresponding to the ferric component, which is readily distinguished from the pyroxene signatures, as these are coupled to a ~2-μm band. Oxides are identified inside Valles Marineris, Terra Meridiani, and Margaritifer Terra (fig. S1).

In Valles Marineris and Margaritifer Terra, oxides are in close spatial association with the sulfate deposits present in these regions (*17*). Figure 2 shows sulfate and oxide association in Capri and Candor Chasma. However, some sulfate deposits do not have the oxide signature [e.g., kieserite deposits in Capri and Gangis Chasmata and the southernmost gypsum deposit in Iani Chaos (*3*, *17*)]. Oxides are more often associated with polyhydrated sulfates than kieserite (e.g., Capri or Juventae Chasma). Exceptions to this rule are found, for example, on the Candor Mensa deposit, where kieserite and oxides are associated. In Terra Meridiani, oxides are identified both in the hematite-bearing plains and in the etched terrains (*18*). No unambiguous sulfate signature is identified in the hematite-bearing plains (*17*, *19*).

Comparison with the mapping of hematite obtained by the Thermal Emission Spectrometer (TES) onboard the Mars Global Surveyor (MGS) reveals important differences (*20*). In Terra Meridiani, OMEGA identifies oxides throughout

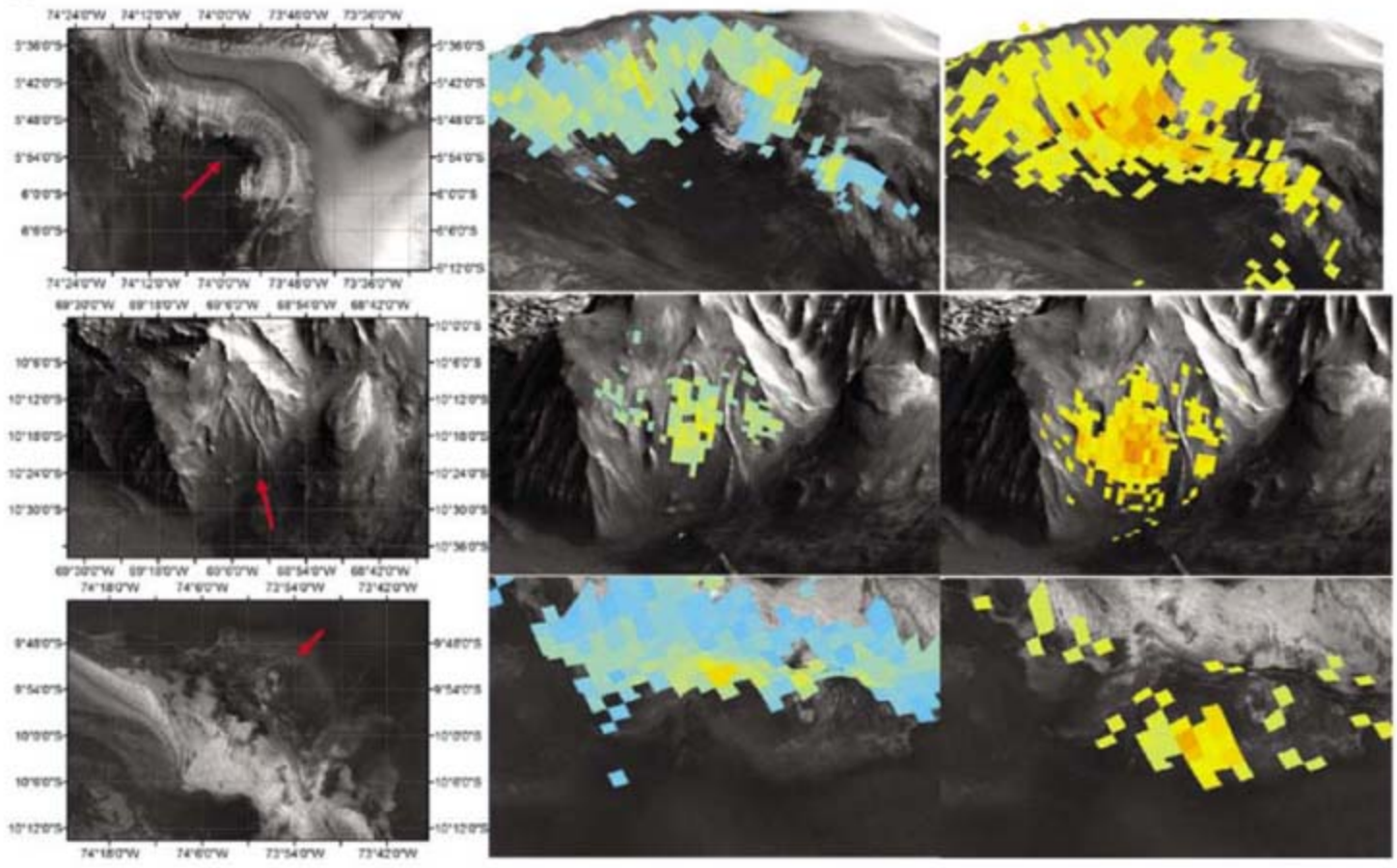

Fig. 3. Oxides and sulfates. (**A**) (Left) Geographic context with the arrow showing the direction of observation chosen for the three-dimensional (3D) views; the center positions are at 5°54′S, 74°W (top); 10°18′S, 69°W (middle); 10°S, 74°W (bottom). (Middle) Sulfate band depth (top: 2.1-μm band for kieserite; middle and bottom: 1.9-μm band for polyhydrated sulfates; blue = 3%, red = 10% and above). (Right) Oxide band depth (yellow = 10%, red ≥ 30%). The images are overlaid on a 3D view of High-Resolution Stereoscopic Camera images from orbits 360, 515, and 334 from top to bottom. (**B**) Distribution of oxides and sulfates versus altimetry in Melas Chasma. The distributions have been normalized by their area for comparison. For example, in the studied area, 8% of the ferric oxides are detected at elevations between −2200 and 2000 m. This diagram shows that oxides are located at similar and lower altimetry than the sulfates on a global scale.

the Etched Terrains and the hematite-bearing plains, whereas TES identifies hematite only in the hematite-bearing plains (*18*, *20*). In Valles Marineris, OMEGA identifications match TES identifications for some spots but not all (*20*). In Aram Chaos, the distribution of oxides as seen by OMEGA is very similar to the distribution of hematite identified by TES. Differences can occur because the visible and near-infrared wavelength range is most sensitive to red hematite, whereas the thermal infrared is most sensitive to coarse-grained hematite, which can be gray in color and not readily detectable at shorter wavelengths (*8*). It is also notable that a ferric absorption was identified in the Infrared Spectrometer for Mars/Phobos2 data (*21*), which matches the location of the westernmost deposit identified here in Candor Chasma.

Comparing ferric oxides with MGS/Mars Orbiter Laser Altimeter (*22*), MGS/Mars Orbiter Camera (*23*), and Odyssey/Thermal Emission Imaging System (*24*) images shows that the ferric oxides are associated with sulfate-rich interior layered deposits (ILDs) and extend to their base as low-albedo sand (Fig. 3). One layered deposit in Capri Chasma demonstrates this relationship particularly well (Fig. 4). Oxide-rich sand dunes are observed at the base of the ILDs. In Candor Chasma, oxide-rich sand is found as far as 2 km away from the base of the ILDs. This suggests that oxide-rich material is sand sized and is sufficiently resistant to survive long-distance transport. It seems that they are originally present in some ILDs and that erosion removal of soft sulfate concentrates ferric oxide.

Ferric oxides are identified by OMEGA over most of the martian surface (*3*); however, their spectral features differ substantially. The ferric oxides identified in the specific and distinct deposits discussed here show spectral signatures up to five times as deep as that of the anhydrous nanophase oxides constituting the bright dust, and they are spatially located and closely associated with sulfate deposits. We cannot entirely rule out that the differences merely reflect a much lower concentration of sulfates in the dust, to a level precluding the spectral features to be observed by OMEGA. Imaging at higher spatial resolution with the Compact Reconnaissance Imaging Spectrometer for MARS/Mars Reconnaissance Orbiter might validate this possibility. Our interpretation of OMEGA data favors a different formation mechanism for the ferric oxides observed in the dust and in the localized deposits described here.

Gas-solid interaction has been identified as a possible mechanism to form the nanophase oxides observed in martian bright regions (*3*). If gas-solid interaction was the principal process that produced these deposits, then one would expect that all light-toned deposits would be affected, which is not consistent with our observations. Alternatively, ferric oxides may have formed by fluid circulation at the surface or subsurface in many different environments (such as volcanic and sedimentary), either simultaneously with sulfates or as secondary phases (such as during later diagenetic alteration). They can exhibit a large variety of grain sizes, from nanophase particles in cement to large concretions

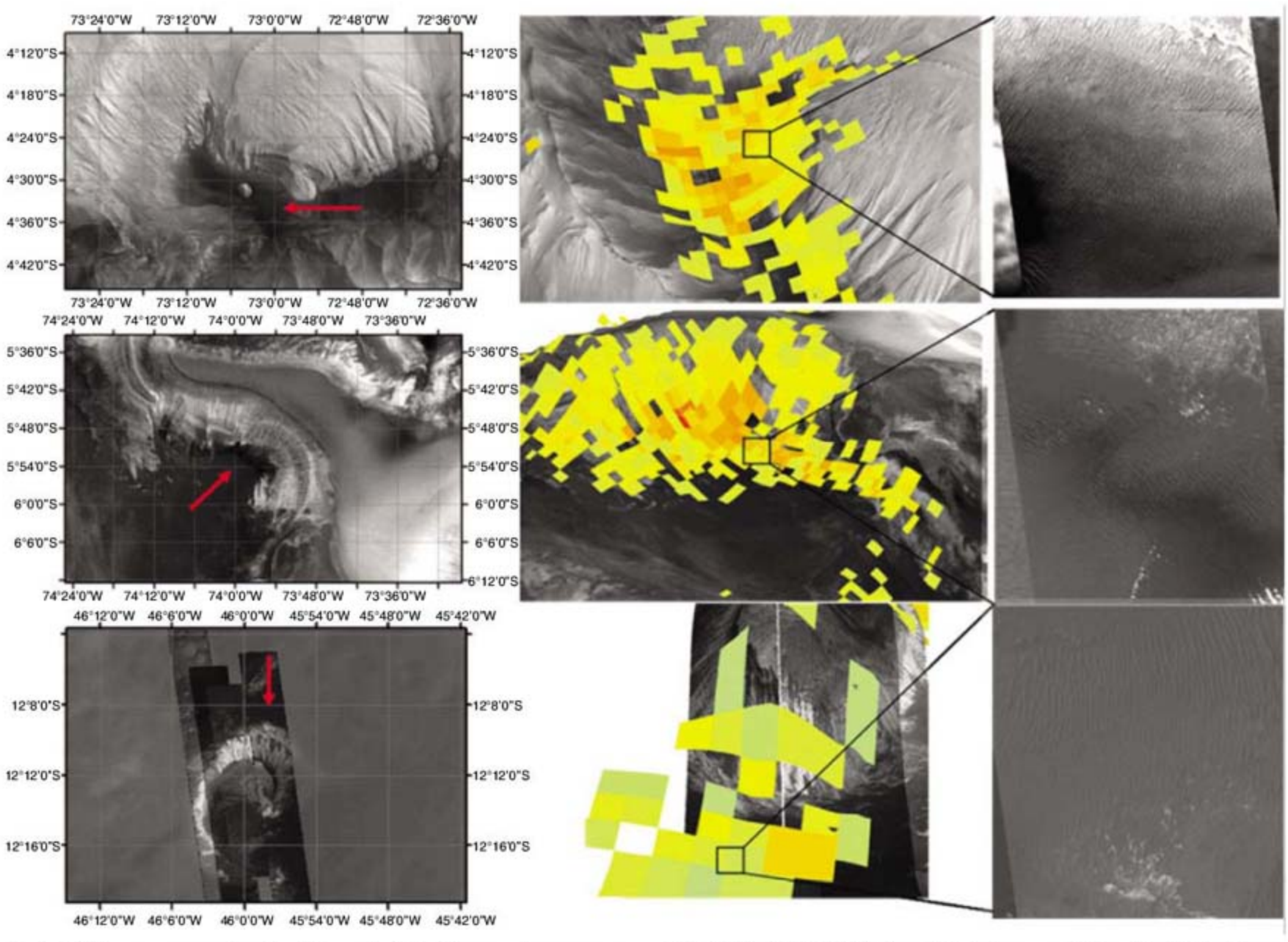

Fig. 4. Oxides are present on the ILDs and at their base, where we can observe oxide-rich sand dunes. (**Left**) Geographic location. The red arrow indicates the direction of observation used for the 3D views; the center positions are at 4°30′S, 73°W (top); 5°54′S, 74°W (middle); 12°12′S, 46°W (bottom). (**Middle**) Views in 3D of areas of interest in Ophir Chasma (top), Candor Chasma (middle), and Capri Chasma (bottom). The oxide band depth is shown on a scale of yellow (10%) to red (≥30%). (**Right**) MOC images showing that oxides are also located in sand-rich areas.

centimetric in size (*25*). Acidic environments have been suggested during sulfate formation in Meridiani Planum (*11*) and Valles Marineris (*3*). Oxide formation is observed together with sulfate precipitation in acidic environments (*26*, *27*). Hematite and sulfate formation are observed during hydrothermal alteration of basaltic tephra under acid-sulfate conditions on Mauna Kea volcano, Hawaii (*28*). Alternatively, diagenesis resulting from iron-rich fluid circulation can lead to large amounts of hematite cement or concretions (*25*). This has been interpreted in Terra Meridiani by the Opportunity Rover Team (*11*), where oxide formation occurs after sulfate formation (*29*, *30*). Sulfates are observed in Valles Marineris on outcrops several kilometers thick, much thicker than in Terra Meridiani, which could have favored sulfate transformation through diagenesis. The presence of concretions in Valles Marineris, although not necessary, would account for all the observations: oxide signature (*31*), resistant material, and accumulation in dark sand. The erosion of sulfate-rich outcrops would have led to the accumulation of oxide concretions at lower altitudes.

Identification of spatial relationships between iron oxides and layered sulfate deposits within Valles Marineris and Margaritifer Terra, which mirror that observed at Meridiani both from orbit and in situ, is a strong indication that these minerals formed in close association, through a process that operated within a specific region of Mars. This is consistent with their origin coupled to the tectonic events following the building of Tharsis, with transient supplies of water cementing sulfates and growing concretions (*3*).

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31. The steep raise in reflectance discussed here is located in the 1.0- to 1.4-μm wavelength range, which is outside Panoramic Camera wavelength range.

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Replication Origin Recognition and Deformation by a Heterodimeric Archaeal Orc1 Complex

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The faithful duplication of genetic material depends on essential DNA replication initiation factors. Cellular initiators form higher-order assemblies on replication origins, using adenosine triphosphate (ATP) to locally remodel duplex DNA and facilitate proper loading of synthetic replisomal components. To better understand initiator function, we determined the 3.4 angstrom–resolution structure of an archaeal Cdc6/Orc1 heterodimer bound to origin DNA. The structure demonstrates that, in addition to conventional DNA binding elements, initiators use their AAA+ ATPase domains to recognize origin DNA. Together these interactions establish the polarity of initiator assembly on the origin and induce substantial distortions into origin DNA strands. Biochemical and comparative analyses indicate that AAA+/DNA contacts observed in the structure are dynamic and evolutionarily conserved, suggesting that the complex forms a core component of the basal initiation machinery.

The common modular architecture of replication initiators suggests that initiator function shares a degree of mechanistic conservation across the different domains of life (*1*–*3*). All cellular initiators contain both canonical DNA binding domains and discrete adenosine triphosphatase (ATPase) modules. The conventional DNA binding domains assist in localizing initiators to replication origins, whereas the ATPase elements appear to mediate the higher-order assembly of initiator subunits at the origin (*4*–*12*). The particular ATPase domains used by initiators fall within the broad superfamily of AAA+ proteins, which share an ability to form large multisubunit complexes that reconfigure the structural states of specific target macromolecules (*13*). Precisely how initiators use the AAA+ architecture to remodel origin structure remains unclear; however, initiator complexes have been shown to load replisomal factors onto DNA (*14*, *15*) and to facilitate origin unwinding in bacteria (*5*).

The archaeon *Sulfolobus solfataricus* uses three origins of replication (*oriC1*, *oriC2*, and *oriC3*) (*12*, *16*), with *oriC2* containing binding sites for all three of the organism's Cdc6/Orc1 initiator paralogs (Orc1-1, Orc1-2, and Orc1-3; Fig. 1A) (*17*). Previous studies suggest that Orc1-1 and Orc1-3 bind during the initiation of DNA replication and that Orc1-2 may act as a negative regulator (*12*). Although Orc1-1 recognizes an origin DNA repeat sequence known as the origin recognition box (ORB) (*11*, *12*), as well as a minimized version of this motif (mORB) found at *oriC2*, Orc1-2 and Orc1-3 each bind separate repeat sequences that are distinct from the mORB sites (termed C2 and C3, respectively). A 6–base pair (bp) overlap occurs between a mORB and a C3 site, creating a dual-site sequence jointly recognized by both Orc1-1 and Orc1-3 (Fig. 1A and fig. S1). To understand the molecular determinants by which initiators recognize and reshape origins, we cocrystallized Orc1-1 and Orc1-3 with a 33-bp DNA encompassing the mORB/C3 dual site (*18*). The structure was solved by multiwavelength anomalous dispersion (MAD) using

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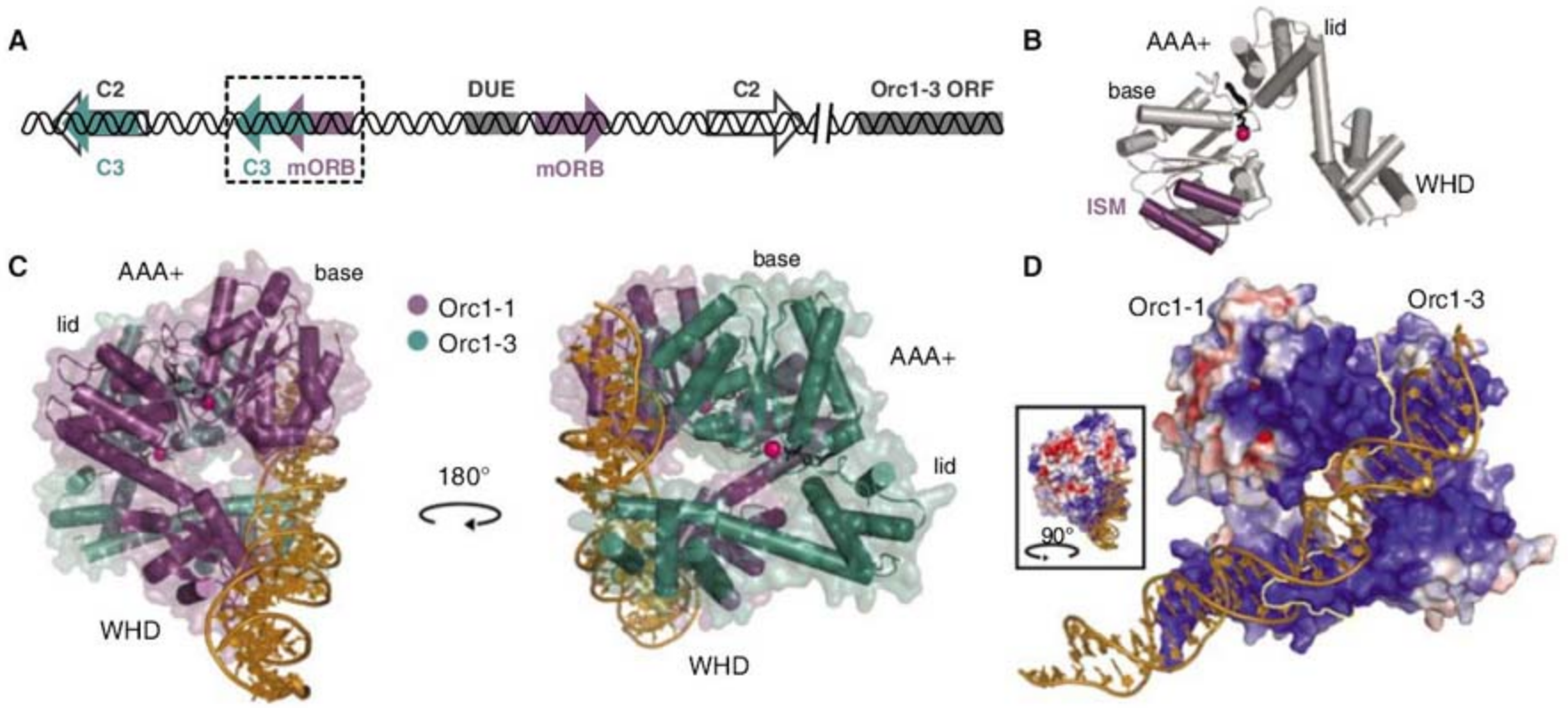

Fig. 1. Initiator/origin complex. (**A**) Schematic of *oriC2*, highlighting sequences recognized by Orc1-1, Orc1-2, and Orc1-3 paralogs (purple, gray, and teal arrows, respectively). The direction of the purple arrows reflects the 5′-to-3′ convention of the mORB consensus sequence; the C2- and C3-site arrows indicate the relative orientations of these repeats. The dashed box denotes the C3/mORB dual site used in the cocrystal structure. DUE, DNA unwinding element. (**B**) A cartoon of Orc1-1 illustrates the relative orientation of the initiator's subdomains, with the ISM of the AAA+ domain in purple. ADP, black sticks; magnesium ion, magenta sphere. (**C**) Global architecture of the Orc1-1/Orc1-3•DNA complex. Protein, purple and teal; DNA, orange; ADP, black sticks; magnesium ions, magenta spheres. (**D**) Electrostatic surface representations of Orc1-1 and Orc1-3. The yellow line demarcates the boundary between protomers.

a selenomethionine-substituted sample, and the final model was refined to an R_{free} of 26.9% (fig. S2 and table S1) (*18*).

Both initiators demonstrate similar overall architectures, with winged-helix domains (WHDs) adjacent to, but offset from, the conventional oligomerization surfaces of the AAA+ ATPase modules (Fig. 1B and fig. S3). This configuration gives the initiators the appearance of a pair of lobster claws, which sit side by side to grip the DNA (Fig. 1, C and D). Although Orc1-1 and Orc1-3 share only a 360 Å^2 interface, the juxtaposition of the two initiators creates a continuous swath of positively charged surface that binds a 28-bp stretch of DNA and buries over 2500 Å^2 in the nucleoprotein interface (Fig. 1D). The WHD and the AAA+ domain of each protein contribute to DNA binding.

The Orc1-1 and Orc1-3 WHDs bind in a nearly identical manner along a single face of the DNA (Figs. 1, B and C, and 2, A and B). The defining features of WHDs—the helix-turn-helix (HTH) and β-hairpin "wing" motifs—combine to create highly basic faces on the two domains (Fig. 1D), which together provide 75% of the DNA binding surface. In general, these WHDs contact DNA in a canonical fashion (displaying HTH/major groove and wing/minor groove binding), but closer inspection of these interactions reveals notable differences from established WHD binding modes. Most WHD•DNA complexes rely predominantly on one element to bind the major groove of DNA, whereas the second motif plays an auxiliary role in stabilizing the interaction (*19*). In contrast, the HTH and wing of Orc1-1 and Orc1-3 both make major contributions to origin DNA binding by inserting deeply into neighboring DNA grooves (Fig. 2, A and B). The two motifs together bind over a full turn of DNA in a single WHD•DNA interface, an interaction area substantially larger than is seen conventionally for WHDs (fig. S4).

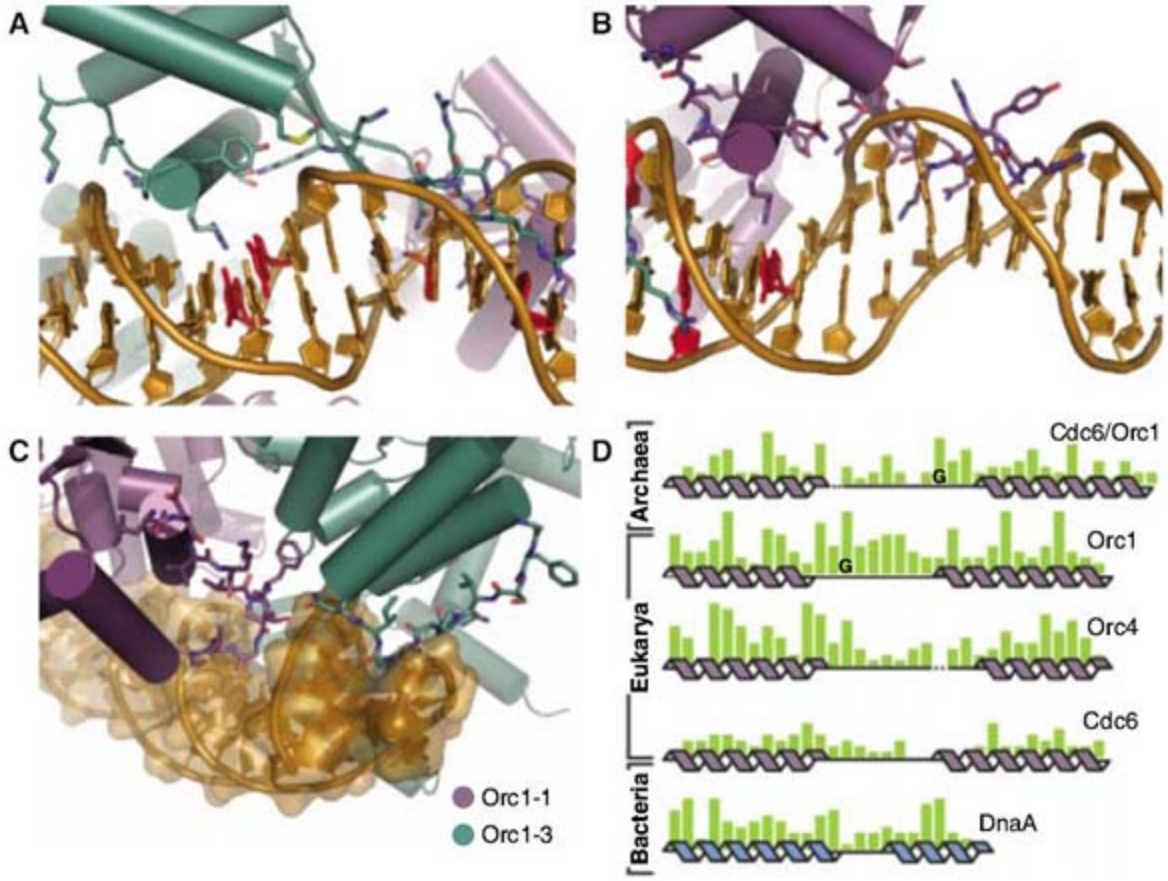

Fig. 2. WHD/DNA and AAA+/DNA interactions. Detailed views of the (**A**) Orc1-3 and (**B**) Orc1-1 WHD•DNA interfaces are shown. Residues within the DNA binding interface are shown as sticks; bases recognized specifically by side chains are red. (**C**) ISMs within Orc1-1 and Orc1-3 AAA+ domains bind adjacent DNA grooves. (**D**) Histograms (green bars) showing the degree of amino acid sequence conservation within the ISMs of archaeal (Cdc6/Orc1), eukaryotic (Orc1, Orc4, and Cdc6), and bacterial (DnaA) initiation factor subclades. Conserved glycines in Cdc6/Orc1 and Orc1 loops are labeled (see also fig. S6).

These contacts play a critical role in mediating initiator/DNA associations, with HTH mutations causing 40- to 400-fold decreases in Orc1-1 and Orc1-3 target site affinities and simultaneous mutation of HTH and wing residues abolishing initiator binding (Fig. 2, A and B, and table S2) (*18*).

The breadth of these initiator WHD•DNA interactions (originally determined by footprinting assays), in combination with the near-palindromic nature of the consensus mORB sequence, initially suggested that initiator WHDs would bind as homodimers to individual origin repeat sequences (*8*, *11*, *12*). Instead, the structure illustrates that a single WHD binds the mORB element in an asymmetric manner, despite the presence of a palindromic sequence motif. The polarity of Orc1-1 and Orc1-3 WHD binding facilitates AAA+ contacts between protomers and with origin DNA sequences 3′ of the WHD-DNA interfaces. Each ATPase domain contacts the DNA using a helix-loop-helix initiator-specific motif (ISM), a distinguishing feature of the initiator clade of AAA+ proteins (Figs. 1B and 2, C and D) (*13*). The Orc1-1 and Orc1-3 initiator insertions contribute to the positively charged AAA+ domain surfaces that bind the phosphate backbone and form additional DNA contacts via the intervening loop within the ISMs. These protein/DNA contacts are nonspecific; however, comparisons of the DNA-bound structures with DNA-free Cdc6/Orc1 structures indicate that the Orc1-1 and Orc1-3 loops undergo a conformational change upon binding to DNA (fig. S5) (*8*, *20*).

The ISMs of archaeal Cdc6/Orc1 proteins show moderate conservation, including a nearly invariant glycine within the ISM loop (Fig. 2D and fig. S6). For Orc1-3, this glycine resides at the bottom of the DNA minor groove, where it adopts a phi/psi backbone geometry that allows the neighboring isoleucine to point inward and pack into the core of the ISM. A similar arrangement is seen in the corresponding Orc1-1 glycine-leucine dipeptide sequence, except that the Orc1-1 loop passes through the major groove using a shallower trajectory. Mutations designed to disturb these loop interactions show a ~70% decrease in the overall affinity for origin DNA, and complete removal of the AAA+ domain substantially weakens initiator binding (table S2) (*8*, *11*, *18*).

Remarkably, Orc1-1 and Orc1-3 achieve selective recognition of their respective target sites, including the asymmetry of intiator binding, with nominal sequence-specific interactions. Arginine-guanine contacts in the Orc1-1 and Orc1-3 HTH motifs, along with asparagine-guanine and arginine-adenine interactions in the Orc1-3 wing, constitute the only side-chain/base associations in the nucleoprotein interface (Fig. 2, A and B). Although we cannot rule out water-mediated base contacts at this resolution, it appears that nonspecific peptide-backbone/base and side-chain/DNA-backbone interactions form the remainder of the initiator•DNA contacts (fig. S7). Clues to this unusual and seemingly context-dependent recognition of origin sequence come from an analysis of DNA geometry, which shows that Orc1-1 and Orc1-3 both substantially unroll the double helix while preserving base pairing (Fig. 3, A and B, and fig. S8). Methidiumpropyl-EDTA (MPE) and copper phenanthroline (Cu-OP) footprinting studies (*18*) corroborate these distortions in vitro, with sites of initiator-dependent increases in modification propensity correlating strongly with bend points observed in the structure (fig. S1). These assays also reveal that isolated Orc1-1 binding includes the GGA sequence just 3′ of the *oriC2* mORB site, a region occupied by the Orc1-3 WHD in the heterodimeric complex structure. Association of Orc1-1 with this sequence (which is typically composed of guanines in full-length ORBs) (*11*, *12*) increases chemical probe sensitivity at the site's 3′ end, consistent with the idea that Orc1-1 introduces a bend in this region (fig. S1) (*21*). The addition of Orc1-3 appears to remodel this association, nudging the Orc1-1 AAA+ domain away from the minor groove and into the adjacent major-groove binding conformation observed in the co-crystal structure. Together, Orc-1 and Orc1-3 induce a 20° bend in the DNA duplex at the point where their binding sites overlap (Fig. 3B).

The structure of the complex thus reveals that the two initiators work individually and collectively to introduce local and global DNA deformations that substantially underwind the origin (Fig. 3, A and B). Protein/DNA interactions are quite nonspecific across the entire nucleoprotein interface, suggesting that Cdc6/Orc1 proteins rely heavily on sequence context and DNA deformability for origin recognition. In this regard, the behavior of the archaeal initiators appears to lie midway on a continuum of origin-binding mechanisms that range from the highly specific recognition of conserved sequence repeats by the bacterial DnaA initiator (*22*) to the complete absence of distinct origin sequences for origin recognition complex binding in metazoans (*23*). Using DNA malleability as a means of origin recognition could allow archaeal initiators to bind a variety of

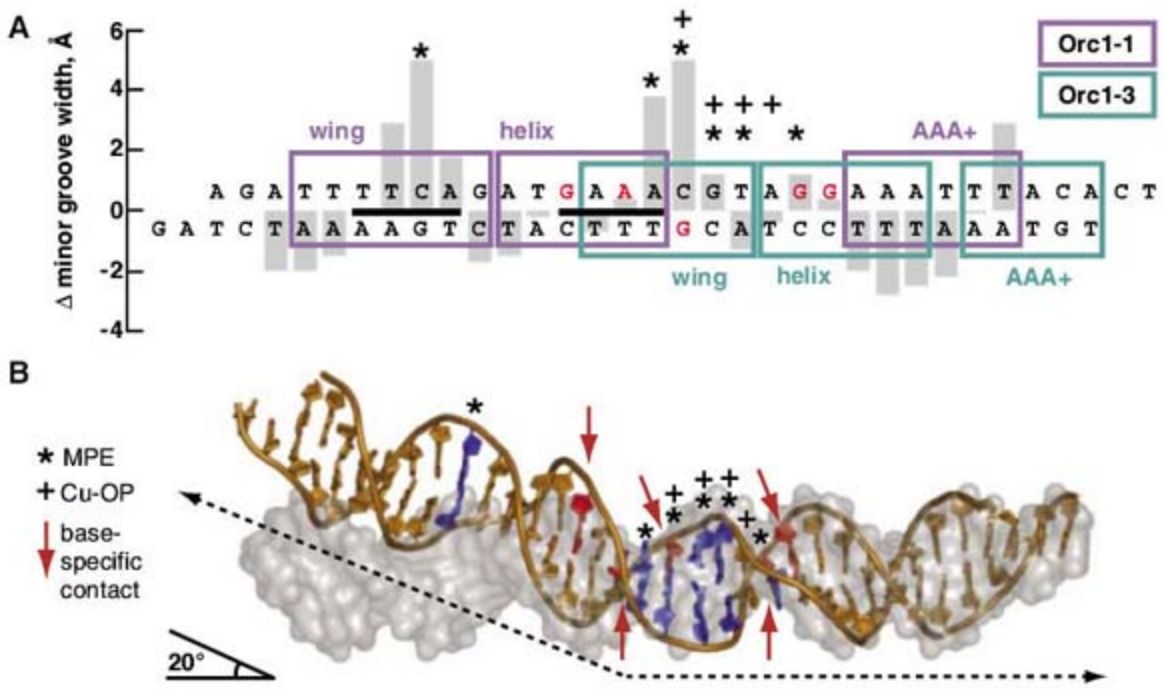

Fig. 3. Initiators deform origin DNA. (**A**) Overview of DNA distortions. Highly conserved mORB sequence positions are underlined. Bases specifically recognized by side chains are in red. Distortion (Δ) of the minor groove width from idealized B-form DNA is plotted in gray along the DNA sequence. Positions sensitive to MPE (asterisks) and Cu-OP (crosses) modification in the presence of Orc1-1 and Orc1-3 correspond with deformations seen in the structure (fig. S1). (**B**) Comparison between initiator-bound (orange cartoon) and B-form (gray surface) DNA. Base pairs sensitive to MPE and Cu-OP modification are in blue and distinguished as in (A). Bases specifically recognized by side chains are highlighted in red.

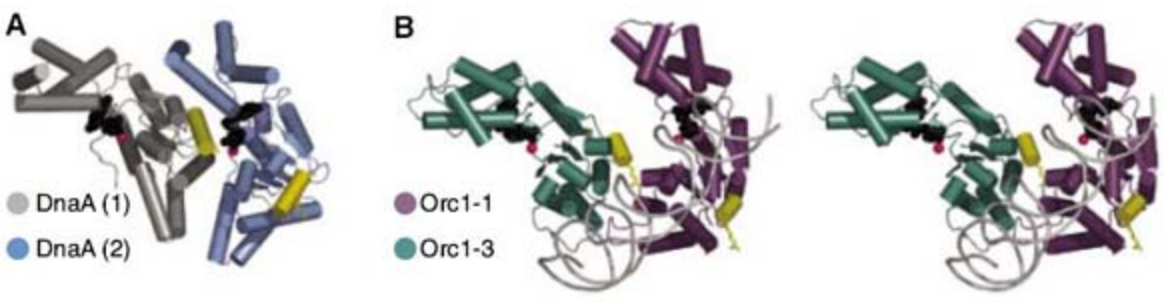

Fig. 4. Initiator AAA+ interactions. (**A**) The AAA+ domains of ATP-bound DnaA (*Aquifex aeolicas*, Protein Data Bank accession number 2HCB) (*24*) assemble in a head-to-tail oligomer that places the arginine finger of the box VII helix (gold) into the ATPase active site of the adjacent protomer. (**B**) Stereo view of the Orc1-1/Orc1-3•DNA complex shows that contacts between adenosine diphosphate–bound initiators and DNA orient successive AAA+ domains into a similar, albeit more open, configuration to that of oligomerized DnaA. For clarity, only initiator AAA+ domains are shown in (A) and (B). Bound nucleotides (black) and magnesium ions (magenta) are shown as spheres.

origin sequences and may promote the melting of DNA strands required for origin unwinding.

Although direct contacts between Orc1-1 and Orc1-3 are sparse, these proteins influence one another's DNA binding activities (fig. S1), indicating that initiators associate with target sites in a dynamic manner that can be modulated by other initiator subunits. In this respect, it is notable that initiators are AAA+ proteins, which typically assemble into higher-order complexes that form bipartite ATPase active sites between subunits. A key set of ATPase interactions is exemplified by DnaA (Fig. 4A), in which an arginine finger from a conserved AAA+ element (the box VII motif) inserts into the γ-PO_4 binding cleft of an adjacent protomer to stimulate ATP hydrolysis in trans (*24*). In the ADP-bound Orc1-1/Orc1-3 complex, the two initiators align on DNA in a head-to-tail arrangement similar to that seen in other AAA+ proteins, positioning the box VII helix of Orc1-3 near the active site of Orc1-1 (Fig. 4B and fig. S9). This binding of the Cdc6/Orc1 initiators to DNA appears to set up a conformation that poises the ATPase machinery to accept subunit-docking events that would lead to higher-order complex formation upon ATP activation.

A particularly unexpected feature of the structure is the ability of the initiator ATPase domain to bind DNA. Phylogenetic analyses show that the ISM sequences are conserved within, but not between, initiator subfamilies, suggesting that this region may help determine the specific function of orthologous and paralogous initator subunits (Fig. 2D and fig. S6) (*13*). Structural comparisons between initiators and other DNA binding AAA+ proteins reveal that ISMs overlap spatially with clade-specific AAA+ elements of proteins that contact nucleic acid in the interior of an oligomeric assembly (fig. S10) (*25*–*27*). Taken together, these findings suggest that the archaeal Orc1-1/Orc1-3•DNA interactions described here form the core of an initiator complex that will self-assemble upon activation to partially or fully encircle DNA during origin firing.

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Supporting Online Material

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Materials and Methods
SOM Text
Figs. S1 to S10
Tables S1 and S2
References
Sequence Alignment Files

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Structural Basis of DNA Replication Origin Recognition by an ORC Protein

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DNA replication in archaea and in eukaryotes share many similarities. We report the structure of an archaeal origin recognition complex protein, ORC1, bound to an origin recognition box, a DNA sequence that is found in multiple copies at replication origins. DNA binding is mediated principally by a C-terminal winged helix domain that inserts deeply into the major and minor grooves, widening them both. However, additional DNA contacts are made with the N-terminal AAA^+ domain, which inserts into the minor groove at a characteristic G-rich sequence, inducing a 35° bend in the duplex and providing directionality to the binding site. Both contact regions also induce substantial unwinding of the DNA. The structure provides insight into the initial step in assembly of a replication origin and recruitment of minichromosome maintenance (MCM) helicase to that origin.

Archaeal DNA replication and repair processes share closer similarity to those in eukaryotes than to those in eubacteria (*1*), albeit with fewer proteins and hence complexity. Furthermore, whereas some archaea have a single replication origin (*2*), others have multiple origins, more like the situation in eukaryotes (*3*, *4*). Archaeal replication origins are recognized by proteins with homology to eukaryotic origin recognition complex (ORC) and Cdc6 proteins (often annotated as ORC/Cdc6 but referred to here as ORC). The number of ORC proteins varies between archaea but is usually one or two proteins, although it can be as many as 14 (*4*).

Crystal structures of two archaeal ORC proteins have been determined (*5*, *6*). The proteins comprise two domains: an AAA^+ domain (*7*) and a C-terminal domain of the winged helix (WH) family, a structural motif commonly used to bind to specific nucleic acid sequences (*8*). The isolated AAA^+ domain retains adenosine triphosphatase (ATPase) activity, and the WH domain binds to DNA (*6*, *9*).

Analysis of archaeal genome sequences revealed a series of short (13 bp) conserved repeats located close to ORC genes that were proposed to be a signature for archaeal replication origins (*10*), which was confirmed experimentally in *Pyrococcus abysii* (*11*, *12*). The later study revealed that two longer repeats were located on either side of an AT-rich region named a duplex unwinding element (DUE). Similar repeats flank a DUE in a region of chromosomal DNA from *Halobacterium* that conveys autonomous replication to plasmids in that species (*13*). These extended repeat sequences were the origin recognition box (ORB) elements later identified at a replication origin in *Sulfolobus solfataricus* (*14*). The ORC1 protein of *S. solfataricus* footprints at these ORB elements in both *P. abyssi* and *Halobacterium*, demonstrating their conservation across species. Curiously, not all of the origins in *Sulfolobus* contain full-length ORB elements but instead have shorter sequences called mini-ORBs (*14*), also found at a proposed origin in *Methanobacterium thermoautotrophicum* (*10*). The situation in *Sulfolobus* is complicated further because the three origins are quite different from one another and they all contain binding sites for multiple ORC proteins (*14*, *15*).

Using the sequence of the conserved ORB elements, Robinson *et al.* proposed the location of a replication origin for *A. pernix* (*14*), which was

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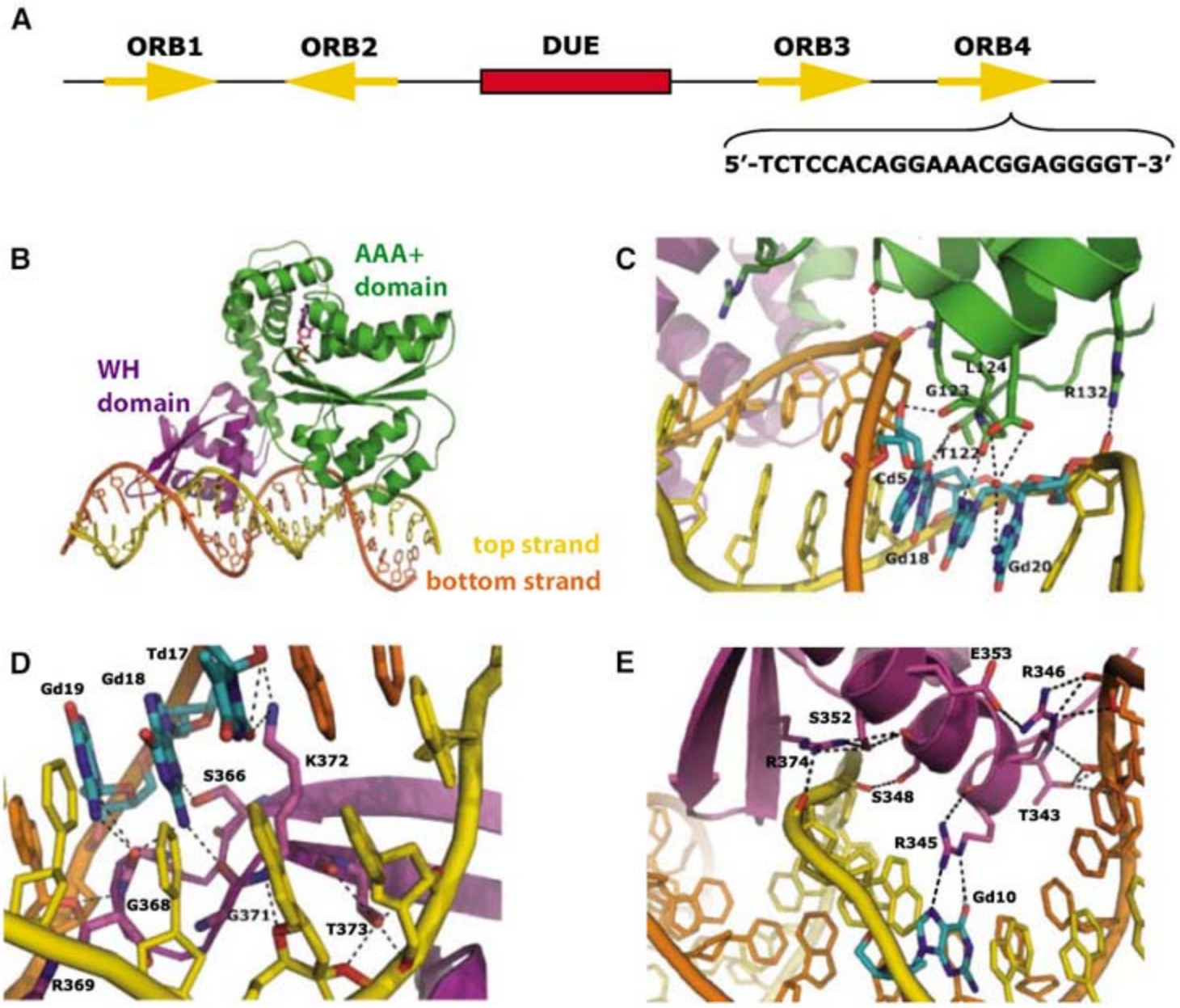


Fig. 1. (**A**) Organization of the *Ori1* replication origin in *A. pernix*. The four ORB sequences are located on either side of the DUE. The sequence of the 5′-to-3′ ("top") strand of ORB4 is shown. (**B**) Overall structure of the ORC1-DNA complex. (**C**) Contacts between the AAA$^+$ domain and DNA. Thr^{122} (T122) (*21*) contacts the Gd18-Cd5 base pair, L124 main chain oxygen contacts Gd19, and E128 contacts Gd20 via a water molecule. Residues T103, R106, G123, and R132 make direct interactions with the phosphodiester backbone on either side of the minor groove. (**D**) Insertion of the wing of the WH domain into the DNA minor groove widens it by 5 Å. Residues S366, G368, G371, and K372 interact directly with bases Td17, Gd18, and Gd19 of the complementary strand. G368, G371, K372, and T373 also interact with the DNA backbone on both sides of the minor groove. (**E**) Insertion of the recognition helix of the WH domain into the major groove. R345 makes a base-specific interaction with Gd10. Residues T343, R346, S348, and R374 contact the DNA phosphate backbone. The R346 side chain is stabilized in a noncanonical conformation by a salt bridge interaction with E353, which enables it to bind the DNA phosphate backbone. In the same way, interaction between S352 and R374 brings the arginine side chain close to the DNA backbone.

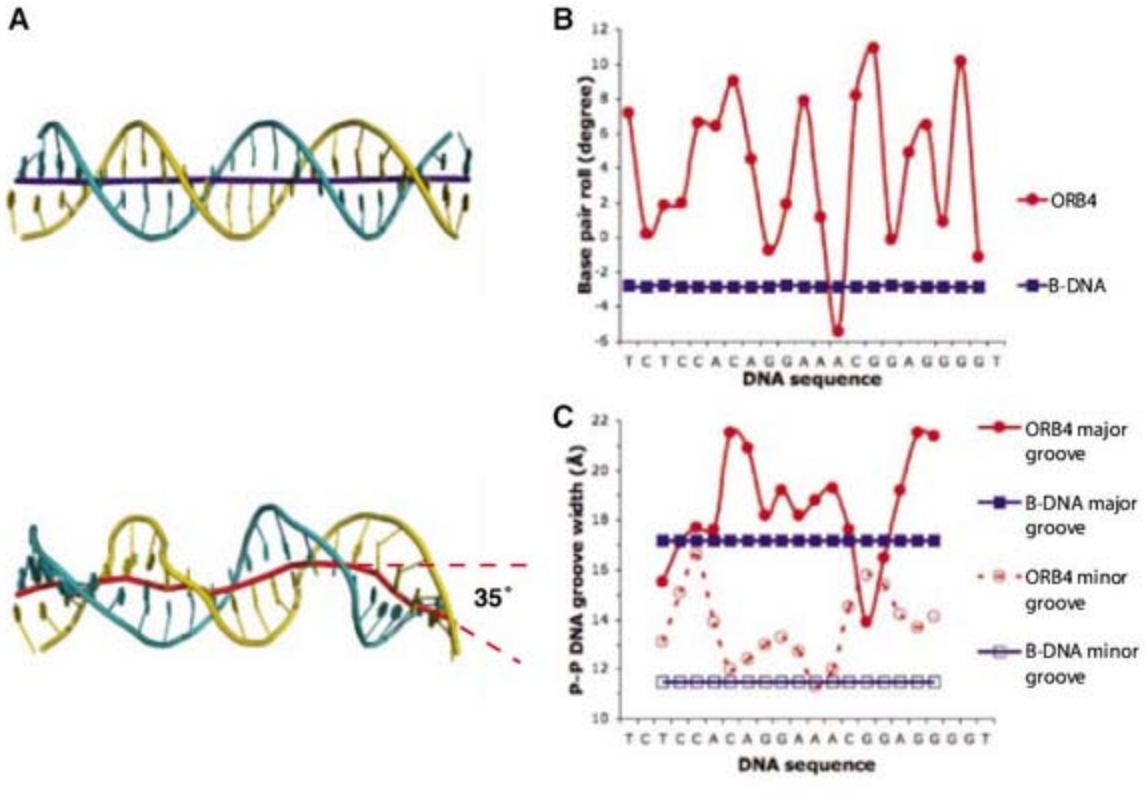
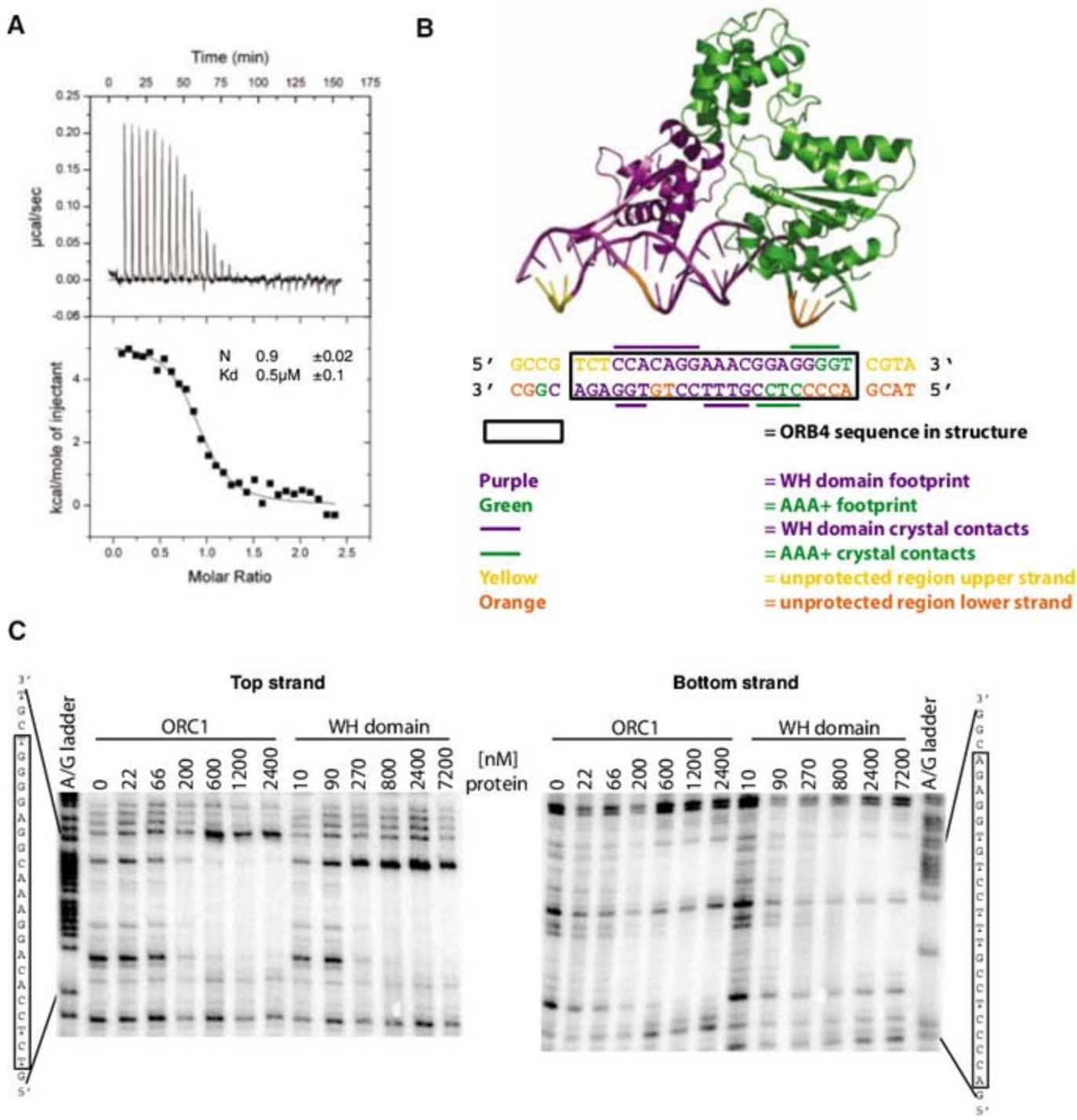


Fig. 2. Deformation of the ORB element compared with regular B-form DNA. (**A**) A comparison between B-form DNA (top) and the ORB4 DNA in the structure (below). The helical axis of the DNA is shown as a blue (B-form DNA) or red (ORB4 DNA) bar running down the center of the duplex. Overall, the DNA is underwound as shown by the twist, which averages 33° per base pair, giving 11 bp per helical turn. DNA parameters were calculated with the program 3DNA (*22*). (**B**) Comparison of the base pair roll for each base pair. The roll is greater for all but one base pair in the ORB4 DNA. (**C**) Comparison of the major and minor groove widths of the ORB element with those for B-form DNA. The minor groove is wider at every position but one along the ORB4 DNA, and the major groove is also wider in all but two places.



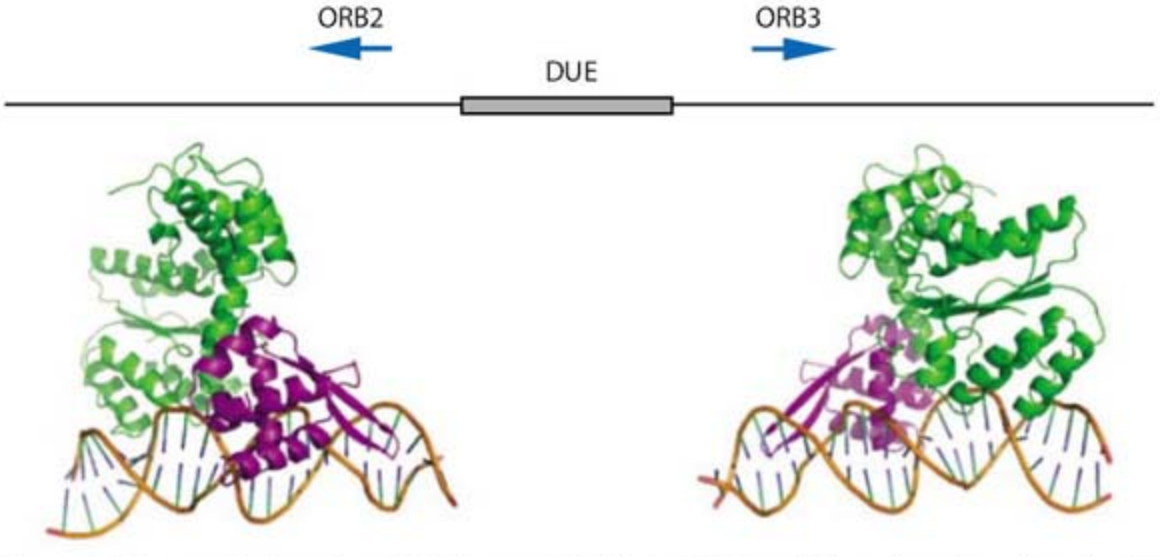


Fig. 3. The stoichiometry of ORC1 binding at the ORB4 element. (**A**) Isothermal calorimetry data collected by using purified WH domain protein and a 40-mer DNA containing an ORB4 element. (**B**) Figure mapping the footprint data [(C)] onto the crystal structure. (**C**) Deoxyribonuclease I footprints across the ORB4 region. DNA sequences are indicated at the side for reference, with the ORB4 sequence boxed.

Fig. 4. ORC1 proteins bound to ORB elements flanking a DUE would be oriented to place the WH domains, which interact with the MCM helicase, facing the DUE and hence the replication start site.

later confirmed (*16*). At this origin (*Ori1*), there are four ORB elements arranged in pairs on either side of a DUE (Fig. 1A). Only one of the two ORC proteins in *A. pernix* (ORC1) binds at the origin. Consequently, *A. pernix Ori1* can be considered an archetype for archaeal replication origins such as the origin in *Pyrococcus* (*12*), the *oriC1* origin of *Sulfolobus* (*14*), at least one of the origins in *Halobacterium* (*13*), and the five origins identified in *Haloferax volcanii* (*4*), all of which contain full-length ORB elements. Similarities with the eukaryotic system also give insight into conserved elements of eukaryotic origin recognition.

To gain an understanding of replication origin assembly, we determined the crystal structure of the *A. pernix* ORC1 protein complexed with a 22–base pair (bp) canonical ORB element (Fig. 1B). The structure of ORC1 is similar to that of other archaeal ORC proteins (*5*, *6*) comprising AAA^+ and WH domains. In common with both previous archaeal ORC protein structures, adenosine diphosphate (ADP) copurifies with the protein (*5*, *6*). The main difference between ORC1 and ORC2 is the region connecting the AAA^+ and WH domains. In ORC2, the flexibility of this region allows the protein to adopt several conformations (*6*). By contrast, the linker in ORC1 is more rigid, a structural difference that is a key element in the interaction between ORC1 and DNA.

The principal contact between ORC1 and its DNA target is with the WH domain, as predicted

by crystal structures (*5*, *6*) and biochemical data (*6*, *9*, *16*–*18*). The WH domain interacts with the ORB sequence in a canonical mode (Fig. 1), with the α helix inserted into the major groove and the wing reaching across the adjacent minor groove, similar to structures seen in other WH domain/DNA complexes (*8*). ORB elements contain a conserved symmetric dyad with a consensus sequence TCCxxxGGA (where x is any base), and mutations in this sequence compromise the ability of ORC1 to recognize ORB elements (*14*). The four ORB elements of *A. pernix Ori1* contain this inverted repeat, which is recognized by the WH domain. Insertion of the recognition helix widens the major groove by over 2 Å, and the central G of the GGA sequence is contacted by an arginine residue (Fig. 1). This arginine is crucial for DNA binding by ORC1 proteins (*14*, *18*, *19*). Several residues contact the phosphodiester backbones across the major groove.

In addition to the recognition helix, the wing plays an important part in the interaction between ORC1 and DNA. The wing is longer than that seen in most WH domains, resulting in an extended contact region that spans five base pairs, including the TCC motif (Fig. 1). The wing inserts deeply into the minor groove, causing it to widen by over 5 Å, and direct contacts are made with the DNA bases. This feature is unusual because the wing in other WH domains merely contacts the phosphodiester backbone over the minor groove. A consequence of this widening of the minor groove is that the protein induces substantial unwinding of the duplex at the binding site (Fig. 2).

The symmetry of WH domain binding-site sequences commonly permits binding of two proteins (*8*). Mutations in the ORB dyad sequence abolish binding of *Sulfolobus* ORC1 to ORB elements (*14*). However, the inverted repeat is located at one end of the conserved ORB element rather than at its center, and there is an additional G-rich sequence flanking it. The crystal structure explains this puzzling feature.

Unexpectedly, there is also a substantial contact between the AAA^+ domain and the DNA. A short loop at the end of an α helix inserts into the minor groove in the region of the conserved guanine residues at the 3′ end of the ORB element (Fig. 1). This region is an insertion into the structure of a canonical AAA^+ domain. This is characteristic of the Clade II AAA^+ proteins that are associated with initiation of DNA replication (*20*). There is only one direct sequence-specific contact and one water-mediated interaction between the AAA^+ domain and the conserved G-rich sequence that it contacts (Fig. 1C). The protein, however, grips one of the DNA phosphodiester backbones through a number of residues. The interaction between the AAA^+ domain and the DNA has two effects. The first is a widening of the minor groove (Fig. 2). The second is that the DNA unwinds as this distortion takes place and is bent by 35°. The extended helix connecting the AAA^+ and WH domains is a key component in this interaction. This rigid connection pushes the AAA^+ domain against the DNA duplex, acting as a brace against which distortion of the DNA can be forced. The net effect of these interactions is extensive unwinding of the DNA. The mean twist per base pair across the DNA is reduced by 3°, resulting in 11 rather than 10 bp per turn and an overall untwisting of over 60° across the ORB element. DNA unwinding is a key aspect in the process of origin assembly.

Although our crystallization conditions contained a ratio of ORC1:DNA of 2:1, our DNA substrate only had a single ORC1 molecule bound. ORC1 forms dimers at higher protein concentrations, and dimerization requires the AAA^+ domain (*16*). Although full-length ORC1 protein is poorly soluble when not bound to DNA, we used the more soluble WH domain to evaluate the stoichiometry of binding at ORB elements using isothermal calorimetry. These data revealed that a single WH domain binds to an ORB element (Fig. 3A), which can be explained by the crystal structure. In canonical WH domain dimers, the wing does not insert into the minor groove. However, in ORC1, insertion of the wing into the minor groove causes it to widen by 5 Å and the associated major groove to narrow by up to 2 Å. Similarly, binding of the helix widens the adjacent major groove by 2 Å. Hence, binding of a symmetric pair at the site requires the major groove to be 4 Å wider than observed, and the recognition helix of a second WH domain cannot be accommodated at the site. Similarly, the associated minor groove would need to widen by over 3 Å to accommodate the wing.

Given the paucity of sequence-specific contacts, particularly those that are not palindromic within the ORB4 sequence, it is unclear how the protein distinguishes sufficiently between the two possible modes of binding. However, of the two possible binding orientations, one is favored by the interaction of the AAA^+ domain with the G-rich sequence, providing a directionality of ORC1 binding at an ORB site. This is important because the WH domain of ORC1 interacts with the mini-chromosome maintenance (MCM) helicase (*19*). Most archaeal origins characterized to date have a pair of inverted ORB elements placed on either side of a DUE in an orientation that would place the WH domains, and hence also the MCM complexes, facing the DUE (*4*, *12*–*14*, *16*), which in *A. pernix* is the location of the replication start site (*16*). Consequently, the G-rich sequence in a full-length ORB element controls the arrangement of ORC1 proteins in an orientation appropriate to interact with MCM helicase during replication initiation (Fig. 4).

To evaluate the contacts observed in our crystal structure, we used DNA footprinting for ORC1 protein and the WH domain alone (Fig. 3). At the 5′ end of the top strand, contacts with the WH domain near the dyad repeat produce footprints that are identical in both cases. The 3′ end of the ORC1 footprint extends four bases further than that of the WH domain alone because of contacts with the AAA^+ domain. On the bottom strand, there is a small region of sensitivity at the center of the footprint. The structure shows that this strand is protected except for the two unprotected bases that are located between the two contact regions made by the WH domain (Fig. 3). The 3′ ends of both footprints are identical but differ at the 5′ end because of contacts made by the AAA^+ domain, extending the footprint by two bases in agreement with the structure. Consequently, the footprints are consistent with the contacts that we observe in the structure, with a single ORC1 molecule binding at an ORB element.

Although we only saw a single ORC1 molecule binding at an ORB, once the initial binding events have taken place then a higher order assembly process begins, the culmination of which is unwinding of the DUE (*16*). The nature of these later events remains unclear but could involve binding of additional ORC1 molecules combined with structural changes in the origin DNA itself. Whatever these changes may be, they likely involve communication between ORC1 monomers, and this may be manifest as the dimer that we saw for the unbound protein at high protein concentrations (*16*). Consequently, although the structure we present here enhances our understanding of the initial stage in this complex process, further work will be required to uncover the structural changes that take place as an origin assembles.

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Supporting Online Material

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Fig. S1
Table S1

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Structure of a Tyrosine Phosphatase Adhesive Interaction Reveals a Spacer-Clamp Mechanism

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Cell-cell contacts are fundamental to multicellular organisms and are subject to exquisite levels of control. Human RPTPμ is a type IIB receptor protein tyrosine phosphatase that both forms an adhesive contact itself and is involved in regulating adhesion by dephosphorylating components of cadherin-catenin complexes. Here we describe a 3.1 angstrom crystal structure of the RPTPμ ectodomain that forms a homophilic trans (antiparallel) dimer with an extended and rigid architecture, matching the dimensions of adherens junctions. Cell surface expression of deletion constructs induces intercellular spacings that correlate with the ectodomain length. These data suggest that the RPTPμ ectodomain acts as a distance gauge and plays a key regulatory function, locking the phosphatase to its appropriate functional location.

The solid tissues of multicellular organisms are held together by interactions between cell adhesion molecules. These molecules can function as nucleation points for multiprotein assemblies that cluster at cell contacts and link to the cellular cytoskeleton. The opposing actions of protein tyrosine kinases and protein tyrosine phosphatases (PTPs) tune the level of tyrosine phosphorylation (*1*–*3*) to control the integrity of such assemblies. Type IIB receptor protein tyrosine phosphatases (RPTPs) combine cell adhesive and catalytic activities in one molecule (*3*) and hence are ideally equipped to act as initial sensors in phosphorylation-based signaling events. Homophilic (trans) interactions control the RPTP subcellular localization (*4*, *5*) and are believed to modulate signaling, but a mechanistic understanding of this process has been lacking.

The type IIB RPTP family (*6*, *7*) consists of four members: RPTPμ, RPTPρ, RPTPκ, and PCP2/RPTPλ. Their extracellular regions are predicted to share a common architecture, comprising six domains: one MAM (meprin/A5/μ) domain, one immunoglobulin (Ig)–like domain, and four fibronectin (FN) type III repeats (Fig. 1A). Our previously reported crystal structure of an N-terminal portion of RPTPμ revealed that the MAM and Ig domains form a structural unit (termed MIg) with a seamless interdomain interface (*8*) but could not explain the biological function of the molecule. Domains beyond MIg are required for cell adhesion (*8*), prompting us to attempt the structural solution of the full extracellular region.

The full-length human RPTPμ extracellular region (eRPTPμ) construct used for structural analysis consisted of residues Glu^{21} to Lys^{742} and contained 12 predicted N-glycosylation sites. To facilitate crystallization, we expressed the protein in glycosylation-impaired mammalian cells, and the resultant oligomannose-type glycans were further trimmed down to single *N*-acetylglucosamine moieties (*9*, *10*). This protein crystallized in space group C2, with one molecule in the asymmetric unit. The structure was solved by molecular replacement and refined to a final R_{work} of 25% (R_{free} = 32%) with diffraction data between 20.0 and 3.1 Å resolution [see (*11*) and table S1]. The crystal structure reveals five well-ordered domains (Fig. 1A): all but the membrane-proximal FN repeat. The MIg structures solved in isolation (*8*) and in the context of the eRPTPμ are essentially identical [root mean square deviation (rmsd) = 1.0 Å for 255 Cα equivalents]; the only notable difference is a reorientation in the Ig domain of some 10° to optimize the interface with the first FN repeat (fig. S1, A and B). The three ordered FN repeats seen in the structure (termed FN1, FN2, and FN3; Fig. 1A) exhibit the classical FN type III topology. The electron density for the fourth FN domain, although sufficient to indicate its approximate position, remained largely disordered throughout refinement; therefore, this domain was not included in the final model (fig. S2, A and B). A pair of FN repeats in the cytoplasmic tail of integrin α6β4 shows particularly strong structural homology with the FN2-FN3 tandem of eRPTPμ [Protein Data Bank (PDB) entry 1QG3; rmsd = 2.1 Å for 170 Cα equivalents] (fig. S1, A and C). Although the sequence identity is only 24%, the residues in the α6β4 tandem FN domain interface and their equivalents in the eRPTPμ FN2-FN3 interface are highly conserved.

The five N-terminal domains of eRPTPμ form a rigid structure, with very short linkers and extensive interdomain interactions (Fig. 1, B to E). As previously reported, the MAM-Ig

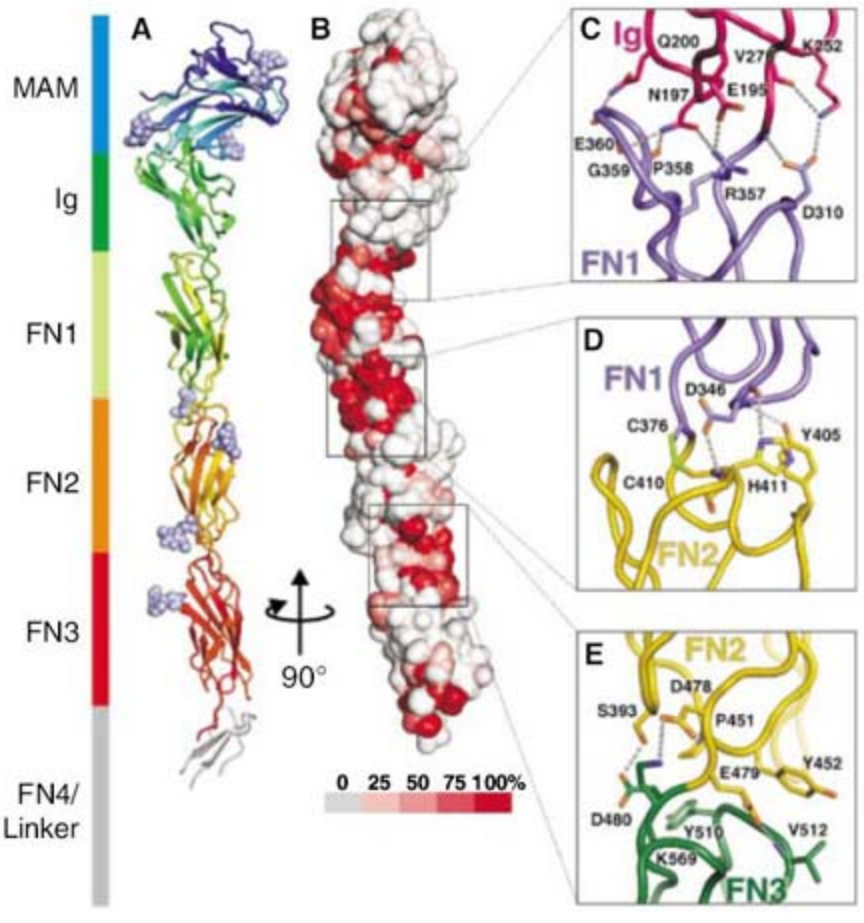

Fig. 1. Structure of the eRPTPμ monomer. (**A**) Ribbon diagram of eRPTPμ, in rainbow coloring (from N terminus in blue to C terminus in red). Sugars are depicted as slate-colored spheres. Modeled parts of the FN4 domain are colored in gray (but are not included in the structure refinement). Domains are indicated schematically at the left of the panel and, in RPTPμ, the ectodomain is followed by a transmembrane helix and two intracellular phosphatase domains. (**B**) Surface representation of eRPTPμ. Coloring is by residue conservation, based on an alignment of 23 sequences (shown in fig. S3A). (**C** to **E**) Close-up views of boxed interdomain junctions from (B). The Ig (magenta), FN1 (slate), FN2 (yellow), and FN3 (green) domains are shown as coils. Residues (*35*) involved in domain-domain interactions are drawn in stick representation (oxygen, red; nitrogen, blue; sulfur, lime). Potential hydrophilic interactions are marked as gray dotted lines.

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interface is spanned by a continuous β sheet (*8*). The Ig-FN1 interface is stabilized by a network of interactions involving primarily polar residues (Fig. 1C), whereas the FN1-FN2 and FN2-FN3 interfaces contain, in addition to multiple potential hydrogen bonds, a disulfide bond and hydrophobic interactions, respectively (Fig. 1, D and E). Typically, all residues involved in these interdomain interactions are strictly conserved within the vertebrate type IIB RPTPs (Fig. 1B and fig. S3, A and B). Thus, this rigid rodlike architecture appears to be a defining characteristic of type IIB RPTP ectodomains. However, specific points of flexion occur in other cell adhesion molecules and may be necessary to allow for limited adjustments in orientation to facilitate cell-cell interactions (*12*). The FN4 domains of RPTPμ and RPTPκ are proteolytically processed in the trans-Golgi network by subtilisin-like protein convertases (*13*, *14*). This cleavage does not lead to release of the molecule from the cell surface (*5*, *13*) but could introduce some flexibility in the membrane-proximal region of the ectodomain. A further point of flexion may be provided by residues linking the FN4 domain to the transmembrane region.

Type II RPTPs are homophilic cell adhesion molecules that form high-affinity dimers in solution (*8*, *15*) and cause cell aggregation when expressed on the surface of normally nonadhesive cells (*16*–*20*). The crystal packing of eRPTPμ reveals an extensive interaction surface between two molecules related by a crystallographic twofold axis (Fig. 2A; buried surface per molecule equals 1630 Å^2 for a probe radius of 1.4 Å). Residues from four domains (MAM, Ig, FN1, and

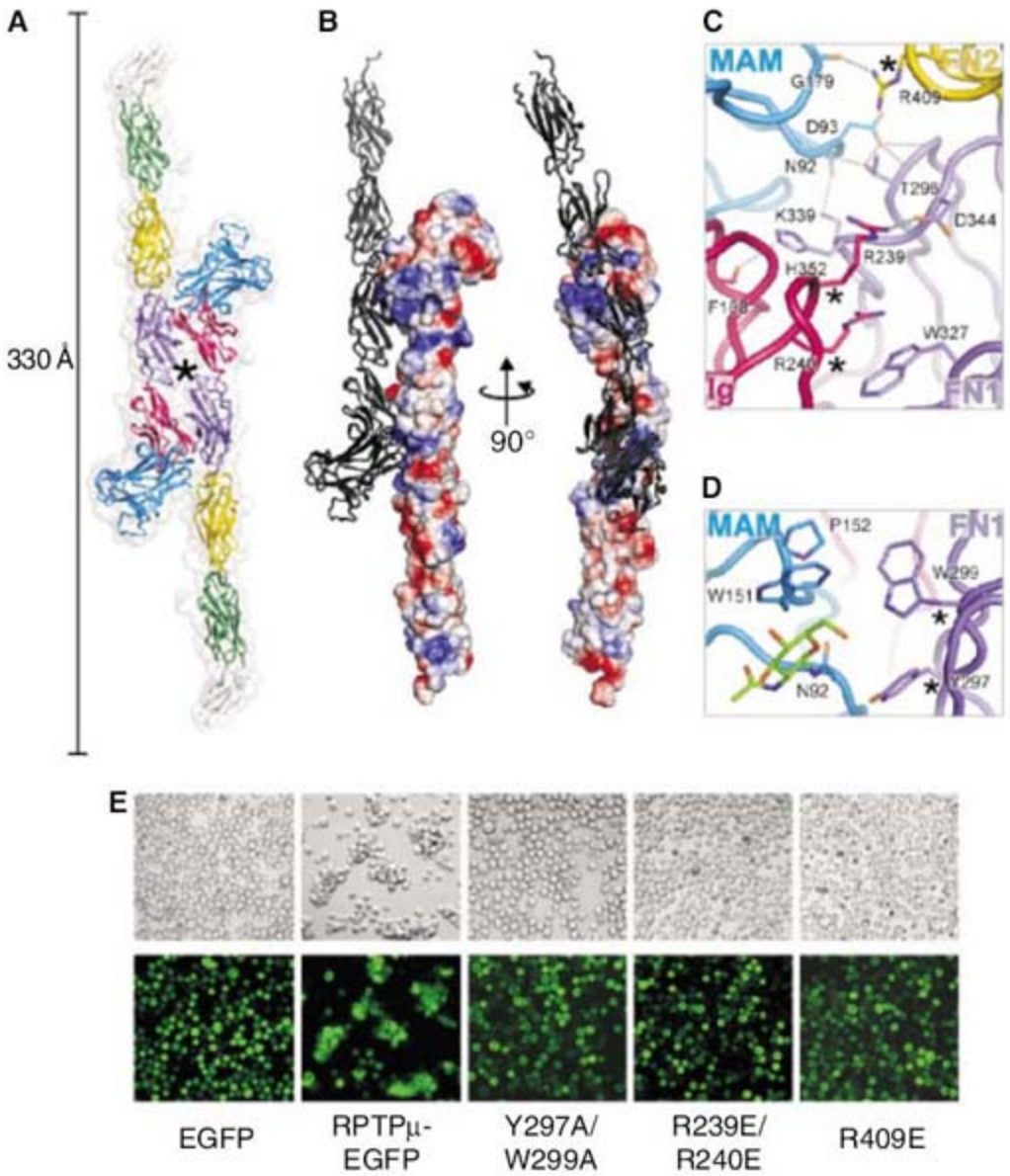

Fig. 2. eRPTPμ dimerization. (**A**) Ribbon diagram of the eRPTPμ dimer. The solvent-accessible surface is drawn in light gray, and the domains appear in blue (MAM), magenta (Ig), slate (FN1), yellow (FN2), green (FN3), and gray (FN4). The asterisk marks the crystallographic twofold axis. (**B**) Electrostatic properties. One monomer is shown as a solvent-accessible surface colored by electrostatic potential contoured at ±10 kT (red, acidic; blue, basic), and the other monomer is shown as a black ribbon. (**C**) The dimer interface. MAM and Ig domains of one molecule interact with FN1 and FN2 domains of another molecule. Domains are colored as in (A). Residues involved in dimer interactions are drawn in stick representation (oxygen, red; nitrogen, blue). Potential hydrophilic interactions are marked as gray dotted lines. Asterisks mark residues targeted for mutagenesis. (**D**) Hydrophobic interactions. Color coding is as in (C), and the N92-linked sugar is colored in green and forms stacking interactions with the indole ring of W151. (**E**) Cell adhesion assays. Nonadherent insect Sf9 cells were infected with baculovirus constructs expressing either enhanced green fluorescent protein (EGFP) alone or RPTPμ-EGFP fusion constructs, wild type and mutant, and observed by phase contrast (top row) and fluorescence (bottom row) microscopy. Formation of aggregates indicates RPTPμ ectodomain adhesive function (*8*).

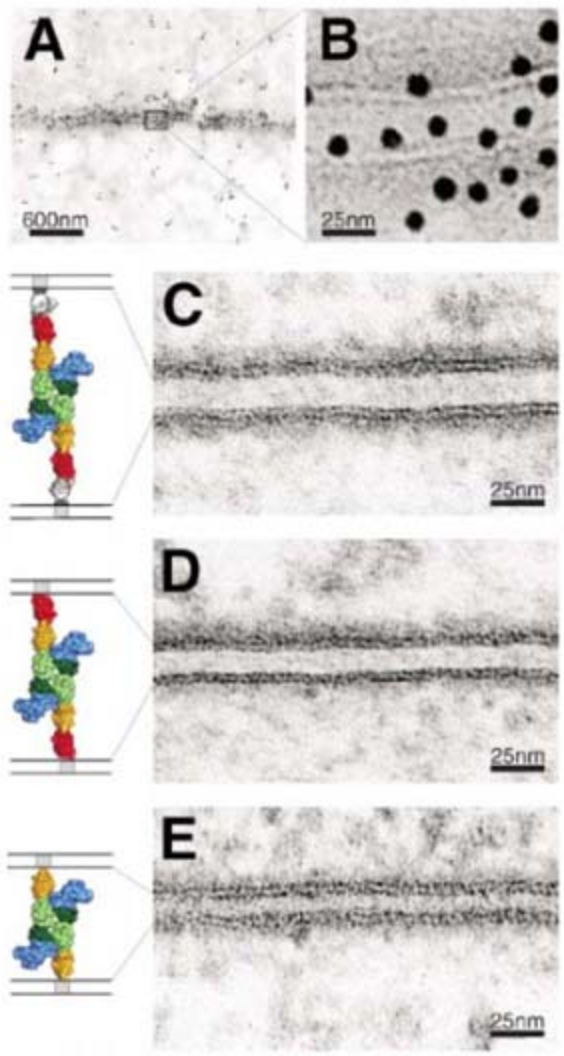

Fig. 3. Ectodomain length of RPTPμ controls intermembrane spacing at homotypic adhesive interfaces. (**A**) RPTPμ accumulation at adhesive interfaces revealed by immuno-EM analysis of cell aggregate cryosections (original magnification, ×23,000). (**B**) Close-up view of an interface region from (A), showing the membrane bilayers (original magnification, ×49,000). (**C** to **E**) Transmembrane RPTPμ constructs induce extensive cell contact regions with aligned plasma membranes (original magnification, ×49,000). The intermembrane distances become progressively shorter as RPTPμ domains are deleted. Measurements (taken at regions of the interfaces where membranes were parallel and clearly defined) reveal the following distances between the extracellular borders of the outer leaflets: 23.7 ± 3.0 nm [n = 115 measurements, from 26 interfaces, one shown in panel (C)], 17.2 ± 1.9 nm [n = 159 measurements, from 32 interfaces, one shown in panel (D)], and 13.1 ± 3.1 nm [n = 114 measurements, from 29 interfaces, one shown in panel (E)]. Intermembrane-distance frequency histograms are provided in fig. S6. Thus, a decrease in cell-cell spacing of ~6 nm between panels (C) and (D) corresponds to the deletion of one FN domain plus the tail region, and a decrease of ~4 nm between panels (D) and (E) corresponds to the deletion of one FN domain, per RPTPμ monomer. The observed full-length RPTPμ-induced intermembrane distance is in agreement with published data on similarly treated samples of cadherin-mediated cell junctions (*30*, *31*).

FN2) contribute to this dimer interface (Fig. 2A), which is mainly hydrophilic, involving 14 potential hydrogen bonds, and which is further stabilized by 24 residues and a glycan per monomer, forming van der Waals contacts (Fig. 2, B to D). The main interaction surface is formed between the MAM and Ig domains from one molecule and the FN1 and FN2 domains from the other. To verify the biological importance of this interface, we performed site-directed mutagenesis of residues (marked by asterisks in Fig. 2, C and D) that appear to play a crucial role for its integrity and are highly conserved within the RPTP family. The oligomeric state of mutant proteins was assessed by size-exclusion chromatography (soluble ectodomain constructs; fig. S4) and in vivo cell adhesion assays (transmembrane constructs; Fig. 2E). Mutations of Arg^{239} and Arg^{240} to glutamate or Tyr^{297} and Trp^{299} to alanine abolished dimerization in both assays. In addition, a FN2 domain mutation (Arg^{409} to glutamate) impaired dimerization in the chromatography assay and completely abolished cell adhesion. This finding concurs with previously published serial deletion data that defined MAM-Ig-FN1-FN2 as the minimal unit required for cell adhesion (*8*).

Type IIB RPTP ectodomains are highly conserved across species and between family members (typically 50 to 60% amino acid identity; fig. S3). Despite this level of sequence conservation, the homophilic interactions of RPTPμ and RPTPκ show strict specificity in cellular assays (*19*). Such behavior suggests an in vivo sorting function for these cell adhesion molecules, as described for cadherins (*2*): a conclusion reinforced by the generally distinct and complementary expression patterns observed during embryonic development (*7*, *21*). The eRPTPμ structure, when coupled with a sequence alignment between RPTP ectodomains, reveals a strictly conserved scaffold of core interactions (Fig. 2, C to E, and fig. S3A), whereas peripheral areas of the dimer interface show substantial variability; these differences are likely to have evolved to provide the specificity for homophilic segregation (fig. S5A). The high level of sequence conservation also allows us to map a series of RPTPρ mutations, found for an analysis of PTPs in human colorectal cancers (*22*), onto the eRPTPμ structure. Although the role of these mutations in tumorigenesis requires investigation, it is clear that one group of them can be predicted to disrupt the MAM or Ig domain folds, whereas a second set may weaken the interdomain junctions and hence perturb the rigidity of the ectodomain (fig. S5B).

Type IIB RPTP substrates are components of the cadherin-catenin complexes at cell contacts (*3*, *23*–*25*), and RPTPμ is known to associate with multiple cadherins (N, E, R, VE) (*26*, *27*), modulating their adhesive properties. The ectodomains of the cadherins also form trans dimers, and our structural analysis reveals a match between the dimensions of the RPTPμ trans dimer and cadherin-mediated cell junctions (*28*–*31*). Cadherins mediate intercellular contacts in organisms ranging from ascidians to humans (*2*). In vertebrates, cadherin-based interactions need to vary in stability from the relatively static contacts in epithelia or vascular endothelia to the more dynamic ones required by neuronal growth cones. Adhesion-sensor molecules, which selectively localize to cadherin-mediated cell contacts, would provide a mechanism by which to modulate the stability of these regions. If the dimensions of the RPTPμ trans dimers are rigidly set to correspond to a particular cell-cell spacing, this adhesion interaction has the potential to act as a spacer clamp, locking the phosphatase activity at the adherens junction.

To test the ability of the RPTPμ trans dimer to function as a spacer clamp, we expressed a series of transmembrane constructs in which the length of the ectodomain was serially reduced (by deletion of FN4 and FN3-FN4) but the adhesive interaction was conserved (*11*). Electron microscopy (EM) of immunolabeled cryosections confirmed that, in this system, the RPTPμ molecules preferentially located to cell-cell interfaces (Fig. 3, A and B). Measurement of the cell-cell interfaces revealed that expression of each construct resulted in a distinct spacing (Fig. 3, C to E, and fig. S6). Furthermore, these distinctive cell-cell spacings correlated with the number of domains in the extracellular region construct and hence with the length of the trans dimer.

Alongside the above observations, several lines of evidence converge to support the importance of size and homophilic adhesive properties for the ectodomain-regulated localization and function of RPTPμ. At low cell density, RPTPμ has an even distribution over the cell surface, whereas in confluent cultures, surface expression increases substantially (threefold) and localization is restricted to cell-cell contacts (*4*, *5*). Because this increase is not due to the up-regulation of gene expression, the protein appears to be "trapped" at cell contacts through homophilic binding (*5*). Del Vecchio and Tonks (*4*) have shown that, in confluent bovine aortic endothelial and Madin-Darby canine kidney cell cultures, RPTPμ is strictly colocalized with cadherins at intercellular contacts and excluded from the narrow spacings of the tight junctions. Moreover, a RPTPμ construct lacking the Ig domain, and therefore unable to establish homophilic interactions, has a diffuse surface expression pattern even in confluent cultures (*4*). This demonstrates that the intracellular region, despite its ability to interact with cadhe-

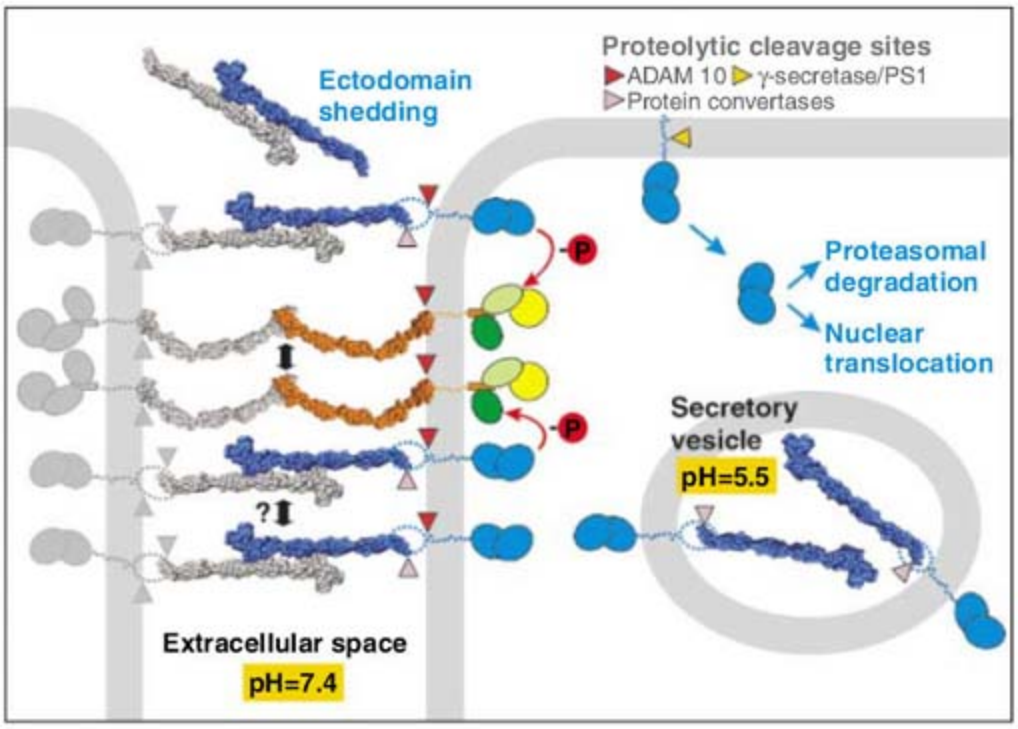

Fig. 4. Model of adhesion-regulated RPTPμ signaling. Cadherins [ectodomains shown in orange, PDB entry 1L3W (*29*)] establish intercellular contacts via trans interactions, as well as cis interactions (black arrow) (*2*, *29*). RPTPμ (shown in blue) trans interactions are pH sensitive (*8*, *18*), which is consistent with the polar nature of the interface, and therefore cannot form at the low pH of the secretory pathway. Cell surface RPTPμ molecules rapidly recirculate, unless there is an appropriate recognition match (*5*). Trans RPTPμ dimerization may be complemented by weak interactions in cis (black arrow and question mark) (*8*, *15*). RPTPμ can stabilize the cadherin-catenin complex [drawn schematically: α-catenin (yellow circles), β-catenin (light green ovals), and p120-catenin (dark green ovals)] by dephosphorylation (*3*) (red arrows). Type IIB RPTPs are processed in multiple proteolytic steps (*5*, *13*, *14*). Protein convertases (in the trans-Golgi network) nick the FN4 domain (*13*, *14*), potentially contributing flexibility. ADAM 10 cleaves close to the membrane (thick gray lines), causing the shedding of RPTPμ (*5*, *14*) and cadherin (*36*) ectodomains. Subsequent γ-secretase–dependent intramembrane cleavage releases the RPTPμ intracellular region (blue ovals) (*14*). The cadherin and RPTPμ ectodomains (crystal structures drawn to the same scale) are shown perpendicular to the cell surface to simplify the figure. EM analysis of adherens junctions and desmosomes has revealed the possibility of non-orthogonal orientations with respect to the membrane surface [with variable tilt angles (*28*, *31*)], but it is not clear to what extent this is caused by sample preparation procedures or flexibility of the juxtamembrane regions.

rins, is not sufficient to colocalize these proteins at the cell junctions. The PTPs generally have little substrate specificity, and they rely on noncatalytic domains to control their subcellular distribution and therefore indirectly regulate their activity by restricting access to particular substrates at defined locations (*6*, *32*). RPTPs are known to be constitutively active, and ligand-induced inactivation has been reported for type I and IV subfamilies. Such a mechanism is unlikely to apply to type IIB RPTPs, where an active enzyme would be required to maintain cadherin-catenin complexes in a dephosphorylated state and thus contribute to the stability of cell contacts (*2*). In this context, for type IIB RPTPs, the ectodomain-mediated trans homophilic interactions appear to represent the driving force for correct localization and function.

Our results on RPTPμ suggest how the type IIB RPTPs modulate the stability of adherens junctions (Fig. 4). The ectodomain trans interaction is switched off at acid pH (*8*, *18*) (i.e., until RPTPμ reaches the cell surface). The rigid, ruler-like ectodomain then acts as a sensor of intercellular distances, matching cadherin-mediated cell contacts, at which point the trans interaction serves as a spacer clamp, locking the phosphatase activity into proximity with the target substrates. The spacer-clamp action of RPTPμ represents the inverse strategy to the size-exclusion mechanism proposed to regulate the cell surface location of another RPTP, CD45; in that case, the mismatch between the RPTP ectodomain and the intercellular spacing is thought to contribute to T cell signaling by expelling the phosphatase activity from local zones of cell-cell contact (*33*, *34*). Unlike CD45, RPTPμ is maintained at cell contacts, potentially increasing the local level of phosphatase activity. Because of the high affinity of the trans interaction, the balance between cell adhesion versus mobility can only be shifted by the action of the ADAM 10 protease (*14*). In both CD45 and RPTPμ, however, ectodomain size and rigidity appear to provide a mechanism to allow cell-cell spacings to regulate intercellular multimolecular assemblies.

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37. Coordinates and structure factors of eRPTPμ have been deposited in the PDB (www.rcsb.org) with the accession number 2V5Y. We thank the staff of the ID 29 beamline at the European Synchrotron Radiation Facility for assistance with data collection; M. Gebbink for the RPTPμ cDNA; P. Reeves and H. G. Khorana for the human embryonic kidney–293S GnTI$^-$ cell line; M. Shaw for assistance with EM imaging; and J. Brown, M. Crispin, W.-C. Hon, and D. Stuart for discussions. The work was funded by Cancer Research UK (CR-UK). E.Y.J. is a CR-UK Principal Research Fellow.

Supporting Online Material

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A MicroRNA Feedback Circuit in Midbrain Dopamine Neurons

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MicroRNAs (miRNAs) are evolutionarily conserved, 18- to 25-nucleotide, non–protein coding transcripts that posttranscriptionally regulate gene expression during development. miRNAs also occur in postmitotic cells, such as neurons in the mammalian central nervous system, but their function is less well characterized. We investigated the role of miRNAs in mammalian midbrain dopaminergic neurons (DNs). We identified a miRNA, miR-133b, that is specifically expressed in midbrain DNs and is deficient in midbrain tissue from patients with Parkinson's disease. miR-133b regulates the maturation and function of midbrain DNs within a negative feedback circuit that includes the paired-like homeodomain transcription factor Pitx3. We propose a role for this feedback circuit in the fine-tuning of dopaminergic behaviors such as locomotion.

MicroRNAs (miRNAs) are derived from long primary transcripts through sequential processing by the Drosha ribonuclease and the Dicer enzyme (*1*). In the context of an RNA-induced silencing complex, miRNAs guide the cleavage of target mRNAs and/or inhibit their translation. miRNAs regulate developmental cell fate decisions in the nervous system and elsewhere (*2*).

Midbrain dopaminergic neurons (DNs) play a central role in complex behaviors such as reward and addiction, and these cells are lost in Parkinson's disease. A number of transcription factors have been identified that regulate midbrain DN development, function, and survival (*3*). However, the role of posttranscriptional mechanisms is unknown. To establish a function for miRNAs, we first used an in vitro model system: the differentiation of murine embryonic stem (ES) cells into DNs (*4*, *5*). An ES cell line was obtained that expresses Dicer enzyme conditionally [containing LoxP recombinase sites that flank both chromosomal copies of the Dicer gene, herein termed floxed Dicer (*6*)]. Introduction of Cre recombinase into these cells by lentiviral transduction leads to the deletion of Dicer in nearly 100% of cells (fig. S1A).

ES cultures were differentiated to a midbrain DN phenotype using the embryoid body (EB) protocol (fig. S1B) (*5*, *7*). Cre-mediated deletion of Dicer at a stage when postmitotic DNs first arise led to a nearly complete loss of DN accumulation, as quantified by the expression of markers including tyrosine hydroxylase (TH) (Fig. 1A). Other mature neuronal classes, including GABAergic neurons, were reduced in these

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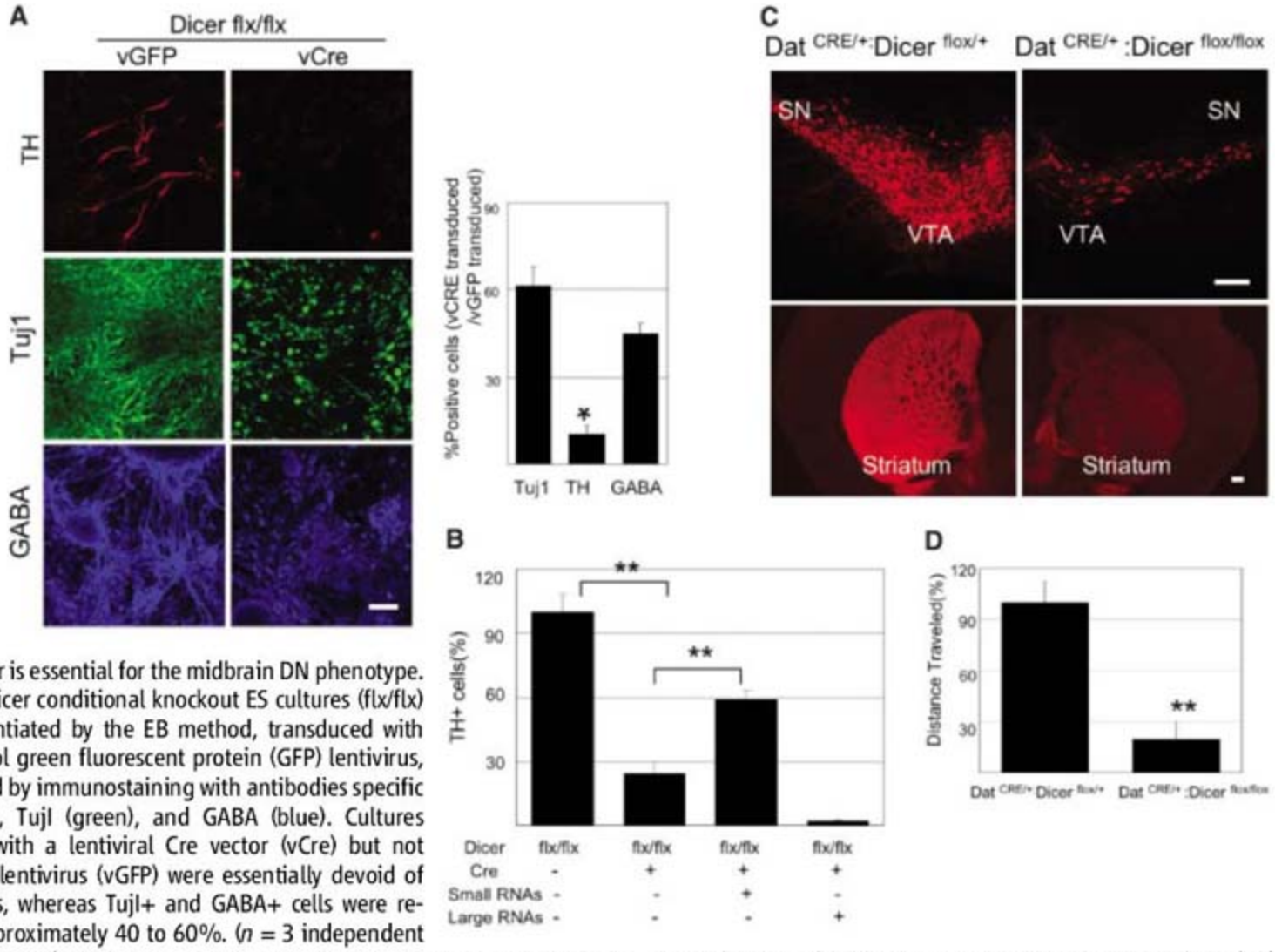

Fig. 1. Dicer is essential for the midbrain DN phenotype. (**A**) Floxed Dicer conditional knockout ES cultures (flx/flx) were differentiated by the EB method, transduced with Cre or control green fluorescent protein (GFP) lentivirus, and analyzed by immunostaining with antibodies specific for TH (red), TujI (green), and GABA (blue). Cultures transduced with a lentiviral Cre vector (vCre) but not control GFP lentivirus (vGFP) were essentially devoid of TH+ neurons, whereas TujI+ and GABA+ cells were reduced by approximately 40 to 60%. ($n = 3$ independent samples per group). Scale bar, 100 μm. Data represent mean ± SEM; analysis of variance (ANOVA) test, $^*P < 0.05$. (**B**) The Dicer deletion phenotype, as in (A), can be "rescued" by transfection of midbrain-derived small RNAs (<200 base pairs) but not large RNAs (>200 base pairs). Two independent experiments of three sets each were performed, with 10 visual fields per set; data represent mean ± SEM; ANOVA test, $^{**}P < 0.01$. (**C**) Immunostaining of brain sections from 8-week-old $DAT^{CRE/+}$:$Dicer^{flox/flox}$ mice for TH demonstrates loss of 90% of midbrain DNs in the substantia nigra (SN) and ventral tegmental area (VTA) and their axonal projections to the striatum relative to control littermates ($DAT^{CRE/+}$:$Dicer^{flox/+}$) ($n = 3$ for each genotype). Scale bars, 200 μm. (**D**) Locomotor activity of $DAT^{CRE/+}$:$Dicer^{flox/flox}$ mice in the open field. The total distance traveled was significantly decreased in $DAT^{CRE/+}$:$Dicer^{flox/flox}$ mice ($n = 4$ for each genotype). Data represent mean ± SEM; Student's t test, $^*P < 0.05$, $^{**}P < 0.01$.

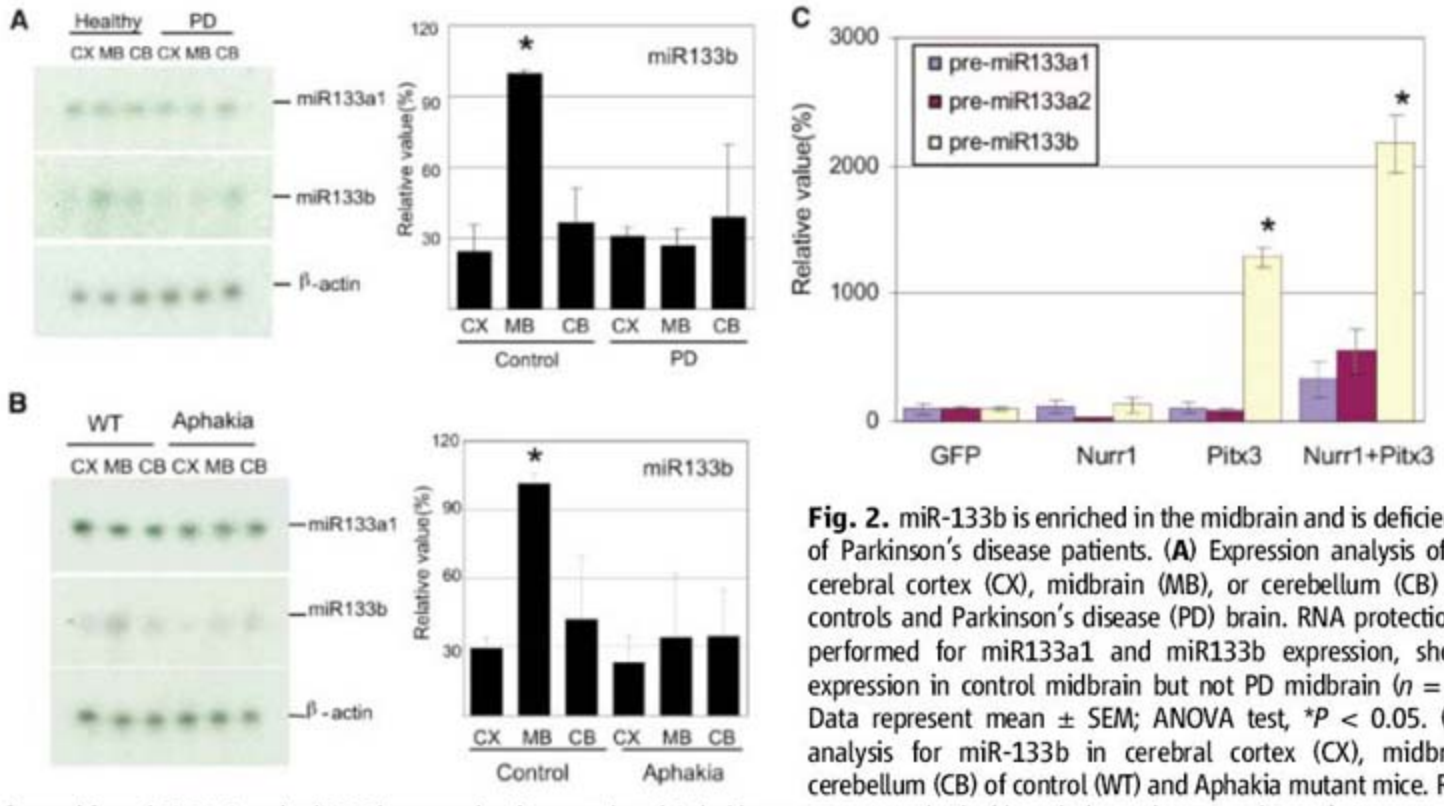

Fig. 2. miR-133b is enriched in the midbrain and is deficient in the tissue of Parkinson's disease patients. (**A**) Expression analysis of miR-133b in cerebral cortex (CX), midbrain (MB), or cerebellum (CB) of unaffected controls and Parkinson's disease (PD) brain. RNA protection assays were performed for miR133a1 and miR133b expression, showing specific expression in control midbrain but not PD midbrain ($n = 3$ per group). Data represent mean ± SEM; ANOVA test, $^*P < 0.05$. (**B**) Expression analysis for miR-133b in cerebral cortex (CX), midbrain (MB), or cerebellum (CB) of control (WT) and Aphakia mutant mice. RNA protection assays were performed for miR133a1 and miR133b expression in control and Aphakia mutant mouse brain (three independent experiments). Data represent mean ± SEM; ANOVA test, $^*P < 0.05$. (**C**) qPCR analysis of murine ES cultures differentiated by the EB method and transduced with lentiviral vectors for *pitx3*, the transcription factor *nurr1* (as a negative control), both, or GFP vector control. Pitx3 transduction leads to the specific induction of miR-133b precursor expression; miR-133a1 and miR-133a2 precursors are not induced by Pitx3 overexpression (three independent experiments were performed). Data represent mean ± SEM; ANOVA test, $^*P < 0.05$.

cultures to a lesser extent (by approximately 50%), as were cells expressing TujI, an early general neuronal marker that first appears at the neural precursor stage of EB differentiation. The Dicer deletion phenotype is partially rescued by transfection of RNA species with low molecular weight (but not high molecular weight) derived from embryonic mouse midbrain, consistent with a model in which miRNAs play a role in midbrain DN terminal differentiation and survival (Fig. 1B and fig. S1D).

To extend these findings to the intact rodent central nervous system, we generated mice that were homozygous for the conditional floxed Dicer allele and expressed Cre recombinase under the regulation of dopamine transporter regulatory sequences [$DAT^{CRE/+}$:$Dicer^{flox/flox}$ (*6*)], leading to the specific deletion of Dicer in postmitotic midbrain DNs (*8*). These mice display a progressive loss of midbrain DNs, as quantified by TH and dopamine transporter (DAT) immunostaining (Fig. 1C and fig. S1E), due to apoptosis (fig. S2A).

Behavioral studies of mice that harbor a midbrain DN-specific deletion of Dicer revealed markedly reduced locomotion in an open-field assay (Fig. 1D and fig. S2B). This is mostly a consequence of long periods of immobility, which is reminiscent of the phenotype of human patients with Parkinson's disease. These results suggest that miRNAs are essential for the terminal differentiation and/or maintenance of multiple neuron types, including midbrain DNs.

Because no specific miRNAs had been implicated in midbrain DNs, we sought to identify some. We took a subtractive approach and compared miRNA expression profiles of the normal adult midbrain with the profiles of a midbrain depleted of DNs. Expression analyses were performed by quantitative real-time reverse transcription polymerase chain reaction (qPCR) for a panel of 224 miRNA precursors in midbrain, cerebellum, and cerebral cortex samples from Parkinson's disease patients and normal controls (fig. S3 and table S1). Expression of one of these precursor miRNAs, miR-133b, was specifically enriched in the midbrain and deficient in the context of Parkinson's disease patient samples, as determined by ribonuclease (RNase) protection assays, qPCR, and Northern blotting for mature miR-133b (Fig. 2A and fig. S4A).

We investigated expression of miR-133b in two additional DN deficiency models: adult Aphakia mice deficient in the transcription factor Pitx3 (*9*–*11*) and mice treated with the DN-specific toxin 6-hydroxydopamine (*5*). miR-133b was specifically expressed in the midbrain of normal mice, as in humans, and expression was markedly reduced in both rodent dopamine-deficiency models as demonstrated by RNase protection assays, qPCR, and Northern blotting (Fig. 2B and fig. S4, B and C).

The relative deficiency of miR-133b expression in Aphakia mouse strain midbrain was surprising, given that adult Aphakia mice do maintain a population of midbrain DNs within the ventral tegmental area (*10*); this suggested the possibility that miR-133b is a direct target of Pitx3 transcription activation (as *pitx3* is mutated in Aphakia mice). Consistent with this model, overexpression of Pitx3 in differentiating ES cultures led to up-regulation of miR-133b precursor expression (Fig. 2C). Furthermore, expression of a luciferase reporter vector that harbors 350 base pairs of proximal miR-133b promoter sequences was specifically induced by overexpression of Pitx3 in COS cells (fig. S4D).

Next, we investigated the consequences of increased miR-133b expression in either ES cell–derived cultures or in primary embryonic day

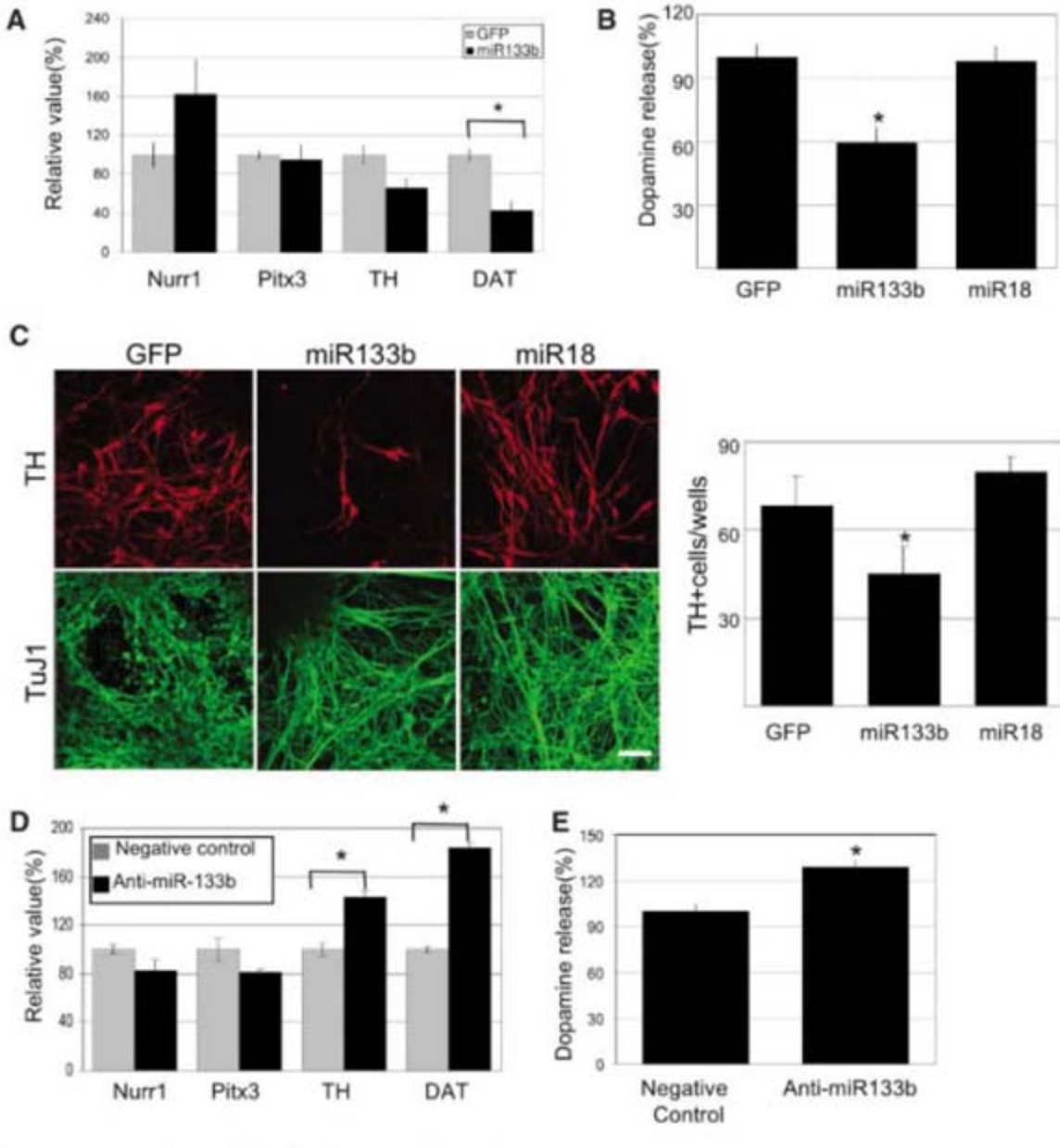

Fig. 3. miR-133b suppresses DN maturation and function. (**A**) Overexpression of miR-133b precursor in primary embryonic rat midbrain cultures led to decreased expression of the mature DN marker, DAT. A lentivirus vector was used to overexpress either miR-133b precursor or control (GFP) sequences. Expression of TH showed a trend toward reduced expression that is not statistically significant, whereas Nurr1 and Pitx3 mRNA expression appeared unaffected. Data represent mean ± SEM; three independent experiments were performed; Student's *t* test, $*P < 0.05$. (**B**) Depolarization-induced dopamine release was quantified in ES-derived, EB differentiated cultures transduced with miR-133b precursor lentiviral vector or GFP control. miR-133b precursor overexpression reduced dopamine release in murine ES culture-derived DNs. Data represent mean ± SEM; five independent experiments were performed; ANOVA test, $*P < 0.05$. (**C**) Overexpression of miR-133b during EB differentiation resulted in a significant decrease in the accumulation of TH-positive cells. Data represent mean ± SEM; three independent experiments were performed; ANOVA test, $*P < 0.05$. (**D**) Reduction of miR-133b by penetratin-conjugated antisense miR133b 2′-*O*-methyl–modified oligonucleotide in primary embryonic rat midbrain culture leads to increased expression of DN mRNAs including TH and DAT, whereas Nurr1 and Pitx3 mRNAs are not significantly altered. Data represent mean ± SEM; five independent experiments were performed; Student's *t* test, $*P < 0.05$. (**E**) Depolarization-induced dopamine release was quantified in murine ES-derived, EB differentiated cultures transduced with miR-133b reduction– (or control-) modified oligonucleotide. miR-133b reduction induced dopamine release in these cultures. Data represent mean ± SEM; three independent experiments were performed; Student's *t* test, $*P < 0.05$.

14.5 (E14.5) midbrain cultures. miR-133b precursor overexpression (using a lentiviral vector; fig. S3A) led to a relative reduction in transcription of the late midbrain DN maturation marker DAT, although transcription of early midbrain DN markers, such as Pitx3 and the transcription factor Nurr1, appeared unaltered or increased (Fig. 3, A and B). Consistent with this, dopamine release in the context of potassium-induced depolarization was markedly reduced with miR-133b overexpression. Overexpression of miR-133b at the neural precursor stage of EB-differentiated ES cultures led to a significant reduction in the number of TH-positive cells (but not TujI-positive cells; Fig. 3C).

The activity of miR-133b can be inhibited using a 2′-*O*-methyl–modified RNA oligonucleotide homologous to the miR-133b sequence and linked to a short peptide derived from the *Drosophila* Antennapedia protein that mediates cell transduction (*12*) (fig. S5A). Suppression of miR-133b in ES cell EB differentiation cultures induced expression of DN markers including DAT and TH (quantified by qPCR analyses; Fig. 3, D and E). In ES-derived cultures, transduction of the miR-133b inhibitory oligonucleotide potentiated potassium-stimulated dopamine release. Taken together, these data implicate miR-133b in the regulation of midbrain DN maturation and function.

Individual miRNAs appear to regulate the expression of numerous targets posttranslationally (*13*). To identify potential physiological targets for miR-133b activity, we used available miRNA target prediction programs based on 3′ untranslated sequence homology to miR-133b (*14*, *15*). The Pitx3 3′-untranslated region (3′ UTR) was identified as a potential target of miR-133b activity, and consistent with this, Pitx3 3′ UTR sequences were subject to suppression by miR-133b when placed downstream of a luciferase reporter gene (fig. S6A). Thus, a hypothetical model for the observed phenotypes associated with altered miR-133b expression is that miR-133b functions within a negative feedback circuit that normally suppresses Pitx3 expression post-transcriptionally, and, in turn, Pitx3 activates midbrain DN gene expression (*5*, *16*) and induces transcription of miR-133b. Fluorescence-activated cell sorter (FACS) analysis of permeablized primary rat midbrain cells with an antibody that recognizes Pitx3 protein revealed that miR-133b overexpression induced a reduction in Pitx3 protein levels in TH+ cells (Fig. 4A), whereas miR-133b reduction led to an increase in Pitx3 protein in TH+ cells (Fig. 4B).

If Pitx3 is a direct target of miR-133b, one prediction is that miR-133b inhibition by modified oligonucleotide transduction would fail to induce TH and DAT expression in Pitx3-deficient, Aphakia primary neuron cultures, and this was observed (Fig. 4C). Finally, FACS analysis on acutely dissociated midbrain DNs from young Dicer mutant mice (10 days old, derived from $DAT^{CRE/+}$:$Dicer^{flox/flox}$ mice) revealed that Pitx3 protein expression is up-regulated in TH-positive neurons (relative to control $DAT^{CRE/+}$:$Dicer^{flox/+}$ cells; Fig. 4D and fig. S6C), consistent with a role for miRNA in Pitx3 regulation.

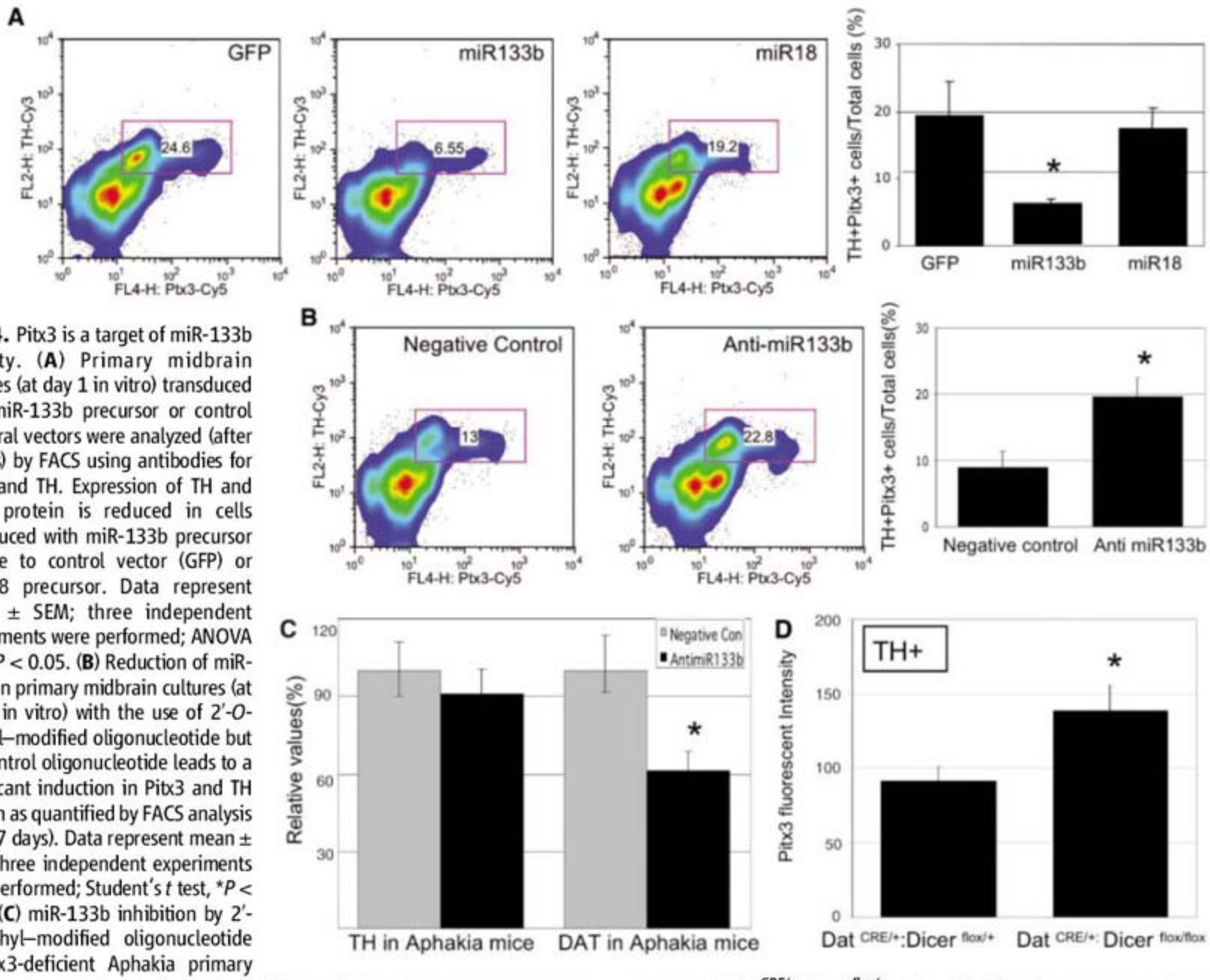

Fig. 4. Pitx3 is a target of miR-133b activity. (**A**) Primary midbrain cultures (at day 1 in vitro) transduced with miR-133b precursor or control lentiviral vectors were analyzed (after 7 days) by FACS using antibodies for Pitx3 and TH. Expression of TH and Pitx3 protein is reduced in cells transduced with miR-133b precursor relative to control vector (GFP) or miR-18 precursor. Data represent mean ± SEM; three independent experiments were performed; ANOVA test, $^*P < 0.05$. (**B**) Reduction of miR-133b in primary midbrain cultures (at day 7 in vitro) with the use of 2′-*O*-methyl–modified oligonucleotide but not control oligonucleotide leads to a significant induction in Pitx3 and TH protein as quantified by FACS analysis (after 7 days). Data represent mean ± SEM; three independent experiments were performed; Student's *t* test, $^*P < 0.05$. (**C**) miR-133b inhibition by 2′-*O*-methyl–modified oligonucleotide in Pitx3-deficient Aphakia primary neuron cultures fails to induce TH or DAT transcription. Data represent mean ± SEM; three independent experiments were performed; Student's *t* test, $^*P < 0.05$. (**D**) Pitx3 protein expression was significantly increased in TH-positive cells from 10-day-old miRNA-deficient $DAT^{CRE/+}$:$Dicer^{flox/flox}$ mice relative to control $DAT^{CRE/+}$:$Dicer^{flox/+}$ mice. FACS analyses were performed on acutely dissociated, permeablized midbrain cells with the use of TH- and Pitx3-specific antibodies. Data represent mean ± SEM; three independent experiments were performed; Student's *t* test, $^*P < 0.05$.

Our data support a model in which miR-133b functions within a feedback loop, as Pitx3 specifically induces transcription of miR-133b, and Pitx3 activity is down-regulated by miR-133b posttranscriptionally (fig. S6D). Midbrain DN function is dynamic, and such feedback circuitry has been shown to increase the robustness and speed response time and stability in the context of dynamic changes (*17*). Furthermore, we present evidence that Dicer deletion leads to the progressive loss of midbrain DNs, suggesting that miRNAs in addition to miR-133b function in these cells.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/317/5842/1220/DC1
Materials and Methods
Figs. S1 to S6
Tables S1 to S3
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Cap-Independent Translation Is Required for Starvation-Induced Differentiation in Yeast

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Cellular internal ribosome entry sites (IRESs) are untranslated segments of mRNA transcripts thought to initiate protein synthesis in response to environmental stresses that prevent canonical 5′ cap–dependent translation. Although numerous cellular mRNAs are proposed to have IRESs, none has a demonstrated physiological function or molecular mechanism. Here we show that seven yeast genes required for invasive growth, a developmental pathway induced by nutrient limitation, contain potent IRESs that require the initiation factor eIF4G for cap-independent translation. In contrast to the RNA structure-based activity of viral IRESs, we show that an unstructured A-rich element mediates internal initiation via recruitment of the poly(A) binding protein (Pab1) to the 5′ untranslated region (UTR) of invasive growth messages. A 5′UTR mutation that impairs IRES activity compromises invasive growth, which indicates that cap-independent translation is required for physiological adaptation to stress.

Translation initiation is a crucial point of regulation of eukaryotic gene expression, allowing cells to adapt rapidly to changing environmental conditions. In response to glucose deprivation, haploid *Saccharomyces cerevisiae* cells dramatically down-regulate translation of most cellular messages, while also exhibiting striking morphological changes leading to invasive growth (*1*, *2*). Whereas the global translational repression requires the mRNA 5′ decapping machinery (*3*), the developmental switch requires new protein synthesis, which suggests that proteins required for invasive growth might be translated by a cap-independent mechanism.

Many invasive growth genes have unusually long 5′ untranslated regions (5′UTRs) with the potential to form stable RNA secondary structures (table S1) (*4*). Furthermore, one gene required for invasive growth, *YMR181c* (*5*), is the downstream open reading frame (ORF) of a naturally occurring bicistronic cellular message (*6*), suggesting that invasive growth genes might be translated by a mechanism that depends on an internal ribosome entry site (IRES). To test whether the 5′UTRs of invasive growth genes are capable of internal translation initiation, we inserted these sequences into a firefly luciferase reporter (F-luc) containing a stable stem-loop structure [change in Gibbs free energy (ΔG°) = –58 kcal/mol] at the 5′ end to inhibit scanning (*7*) and capped with a nonphysiological ApppG cap that reduces binding of the cap-binding initiation factor (eIF4E) by three orders of magnitude (*7*). With no IRES inserted, the ApppG-capped hairpin RNA is poorly translated, yielding 0.4% in vitro and 0.04% in vivo compared with an m7GpppG-capped mRNA (at 100%), with an unstructured 18-nucleotide (nt) 5′UTR (Fig. 1A) (*8*). We confirmed by Northern blots that the reporter mRNAs were stable in both extracts and cells (Fig. 1B), which ruled out differential RNA stability as a source of differences in luciferase activity. Insertion of the 5′UTR sequences from *YMR181c* or from the invasive growth genes *GPR1*, *BOI1*, *FLO8*, *NCE102*, *MSN1*, or *GIC1*, resulted in efficient translation of ApppG-capped hairpin mRNAs compared with length-matched negative control constructs containing reverse-complement 5′UTR sequences. In addition, the 5′UTRs from *TPK2*, *HMS2*, and *YEL033w* lacked IRES activity (Fig. 1C). The invasive growth cellular IRESs' activities ranged from 8 to 33% of that of the control m7GpppG-capped mRNA (table S2). We tested the IRES-containing 5′UTRs for activity in vivo by electroporating the reporter mRNAs into yeast cells to avoid any possibility of mistaking cryptic promoter or splicing activity for IRES activity. All seven 5′UTRs promoted efficient cap-independent translation in vivo (Fig. 1D). Experiments with bicistronic reporters, in which the 5′ ORF is translated via cap-dependent initiation and the 3′ ORF is efficiently translated only when an active IRES is inserted between the two ORFs, corroborated our finding that the 5′UTRs of seven invasive growth genes mediate internal translation initiation (fig. S1).

A subset of viral IRESs recruits the translation machinery by providing high-affinity internal binding sites for the translation initiation factor eIF4G (*9*). To test whether invasive growth IRESs require eIF4G, we prepared extracts genetically depleted of eIF4G (*8*). Reducing eIF4G levels to 37% decreased translation from invasive growth IRES reporters to ~25% activity (Fig. 2A), whereas translation from the eIF4G-independent cricket paralysis virus (CrPV) IRES was only slightly affected. Further depletion abolished activity (fig. S2). In cell extracts containing 9-fold overexpressed eIF4G, invasive growth IRES activity increased 10- to 20-fold (Fig. 2B), which indicated that eIF4G is limiting for IRES activity.

eIF4G is the least abundant initiation factor in yeast (*10*) and becomes unstable in nutrient-limited cells (*11*), which suggests a need for continued synthesis of eIF4G protein in glucose-starved cells in order to maintain invasive growth IRES activity. We therefore tested whether the 5′UTRs from either yeast eIF4G gene are themselves capable of internal initiation

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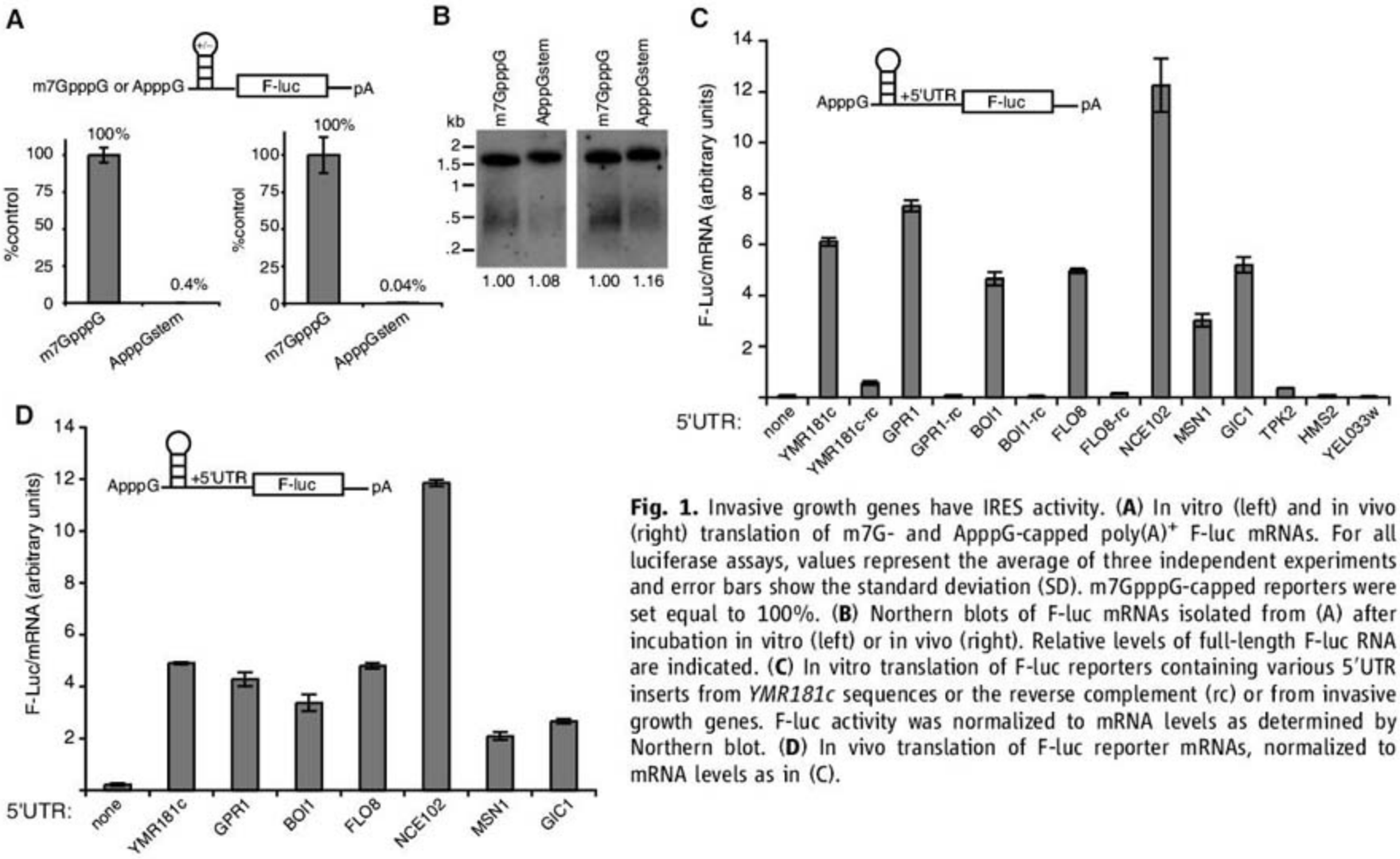

Fig. 1. Invasive growth genes have IRES activity. (**A**) In vitro (left) and in vivo (right) translation of m7G- and ApppG-capped poly(A)$^+$ F-luc mRNAs. For all luciferase assays, values represent the average of three independent experiments and error bars show the standard deviation (SD). m7GpppG-capped reporters were set equal to 100%. (**B**) Northern blots of F-luc mRNAs isolated from (A) after incubation in vitro (left) or in vivo (right). Relative levels of full-length F-luc RNA are indicated. (**C**) In vitro translation of F-luc reporters containing various 5′UTR inserts from *YMR181c* sequences or the reverse complement (rc) or from invasive growth genes. F-luc activity was normalized to mRNA levels as determined by Northern blot. (**D**) In vivo translation of F-luc reporter mRNAs, normalized to mRNA levels as in (C).

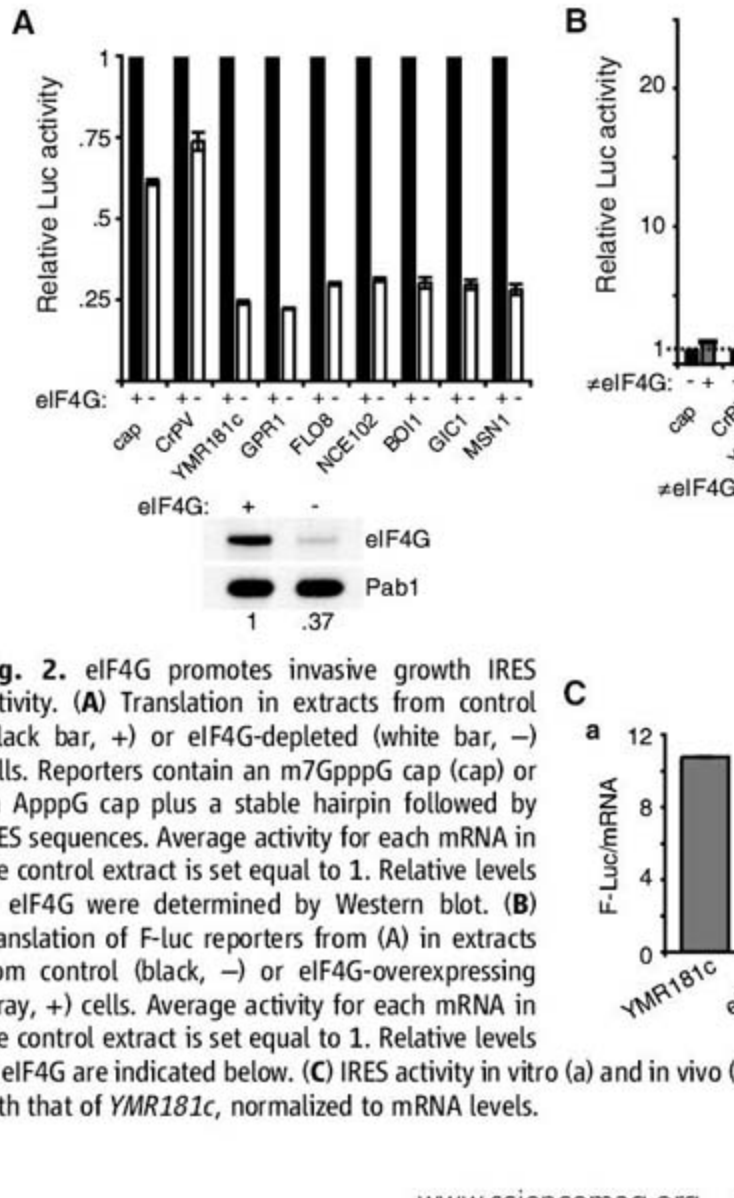

Fig. 2. eIF4G promotes invasive growth IRES activity. (**A**) Translation in extracts from control (black bar, +) or eIF4G-depleted (white bar, –) cells. Reporters contain an m7GpppG cap (cap) or an ApppG cap plus a stable hairpin followed by IRES sequences. Average activity for each mRNA in the control extract is set equal to 1. Relative levels of eIF4G were determined by Western blot. (**B**) Translation of F-luc reporters from (A) in extracts from control (black, –) or eIF4G-overexpressing (gray, +) cells. Average activity for each mRNA in the control extract is set equal to 1. Relative levels of eIF4G are indicated below. (**C**) IRES activity in vitro (a) and in vivo (b) of the 5′UTR of eIF4G2 compared with that of *YMR181c*, normalized to mRNA levels.

using the ApppG-capped hairpin reporter. The 461-nt 5′UTR of eIF4G2 showed IRES activity similar to invasive growth genes' 5′UTRs both in vitro and in vivo (Fig. 2C). Thus, cap-independent synthesis of eIF4G2 could support eIF4G-dependent IRES activity in starved cells.

Well-characterized viral IRESs use disparate strategies for cap-independent recruitment of eIF4G, but many share a requirement for the formation of stable RNA structures (*9*). We performed ribonuclease-mediated structural probing of *YMR181c*'s 298-nt 5′UTR, revealing extensive regions of secondary and tertiary structure (fig. S3). To determine which RNA elements are important for IRES activity, we constructed a series of deletion mutants. Deletion of the structured 5′-most 224 nt had little effect on IRES activity (fig. S4). The 60 nt immediately upstream of the AUG initiation codon were sufficient for robust internal translation initiation (Fig. 3A). This minimal IRES is almost completely unstructured (fig. S3), which suggests a sequence requirement for IRES activity. The minimal IRES sequence includes a polyadenosine [poly(A)] tract (12 out of 13 residues) preceding the AUG initiation codon, reminiscent of the leaders of vaccinia viral mRNAs that are capable of efficient cap-independent translation (*12*, *13*). Deletion of this poly(A) sequence from the *YMR181c* 5′UTR reduced IRES activity both in vitro and in vivo (Fig. 3A). Deletion of the A-tract had no effect on RNA integrity or stability (Fig. 3B).

Poly(A)$^+$ tracts at the 3′ end stimulate eukaryotic translation through conserved poly(A)–binding proteins (PABPs) that enhance translation by at least two mechanisms: stabilizing eIF4G's interaction with the 5′ end of the mRNA through direct interactions between PABP and eIF4G and stimulating 60*S* ribosome subunit joining (*14*, *15*). In principle, both of these functions of PABP could be performed by binding to poly(A) in the 5′UTR. To test the hypothesis that the yeast PABP, Pab1, stimulates cap-independent translation of *YMR181c* specifically through binding to the 5′UTR, we examined translation of mRNAs lacking poly(A) tails. Addition of exogenous poly(A) RNA dramatically inhibited translation of an ApppG-capped hairpin mRNA containing the 5′UTR of *YMR181c*, a defect that was rescued by the addition of recombinant Pab1 (Fig. 3C). Increasing Pab1 concentration specifically enhanced translation from the wild-type *YMR181c* 5′UTR compared with the ΔA mutant IRES or an m7GpppG-capped message lacking a poly(A) tail (Fig. 3D). To test whether Pab1 binds the *YMR181c* 5′UTR directly, we performed filter-binding assays with recombinant protein. Pab1 bound tightly and specifically to the *YMR181c* RNA with an apparent dissociation constant (K_d) of 0.25 ± 0.05 μM, compared with the reverse complement control RNA (K_d = 1.52 ± 0.13 μM); deletion of the poly(A) tract eliminated specific binding (K_d = 3.29 ± 0.41 μM) (Fig. 3E).

Taken together, these data support a mechanism for *YMR181c* IRES activity requiring specific binding of Pab1 to the 5′UTR and suggest that binding of Pab1 to the 5′UTR can functionally substitute for a cap and eIF4E in recruiting eIF4G. This mechanism is not unique to *YMR181c*: The 176-nt 5′UTR from *BOI1* contains a similar AUG-proximal poly(A) tract and requires binding to Pab1 for IRES activity (fig. S5). Notably, we found that the 171-nt 5′UTR of yeast *PAB1* had robust IRES activity in vitro and in vivo (Fig. 3F), and like the invasive growth IRESs, the *PAB1* IRES was strongly eIF4G-dependent (fig. S6). Cap-independent production of both Pab1 (Fig. 3F) and eIF4G (Fig. 2C) could sustain necessary translation during prolonged periods of decreased cap-dependent initiation.

The discovery of IRESs in numerous eukaryotic regulatory genes suggests that IRES-dependent initiation plays a crucial role in cellular adaptation (*16*–*19*). To test this hypothesis directly, we determined whether the *FLO8* IRES is required for *FLO8* function by creating a yeast strain in which the *FLO8* gene was replaced with a mutant version lacking residues –60 to –11 in the 167-nt 5′UTR (*flo8 ΔIRES*). This internal deletion, which removes two poly(A) tracts (fig. S7), reduced IRES-dependent translation of a reporter gene by 60% in vitro (Fig. 4A). Deletion of nucleotides –60 to –11 from the endogenous *FLO8* locus similarly reduced Flo8 protein levels in vivo (Fig. 4B) without affecting *FLO8* mRNA levels (Fig. 4C), consistent with a requirement for IRES activity to maintain wild-type translation. No other feature of the *FLO8* gene was altered. To test whether this reduction in Flo8 is physiologically significant, we assayed the *flo8 ΔIRES* mutant strain for invasive growth and for expression of *FLO11* mRNA, which requires *FLO8* (*20*). The *flo8 ΔIRES* mutant is defective for both invasive growth (Fig. 4D) and for transcription of

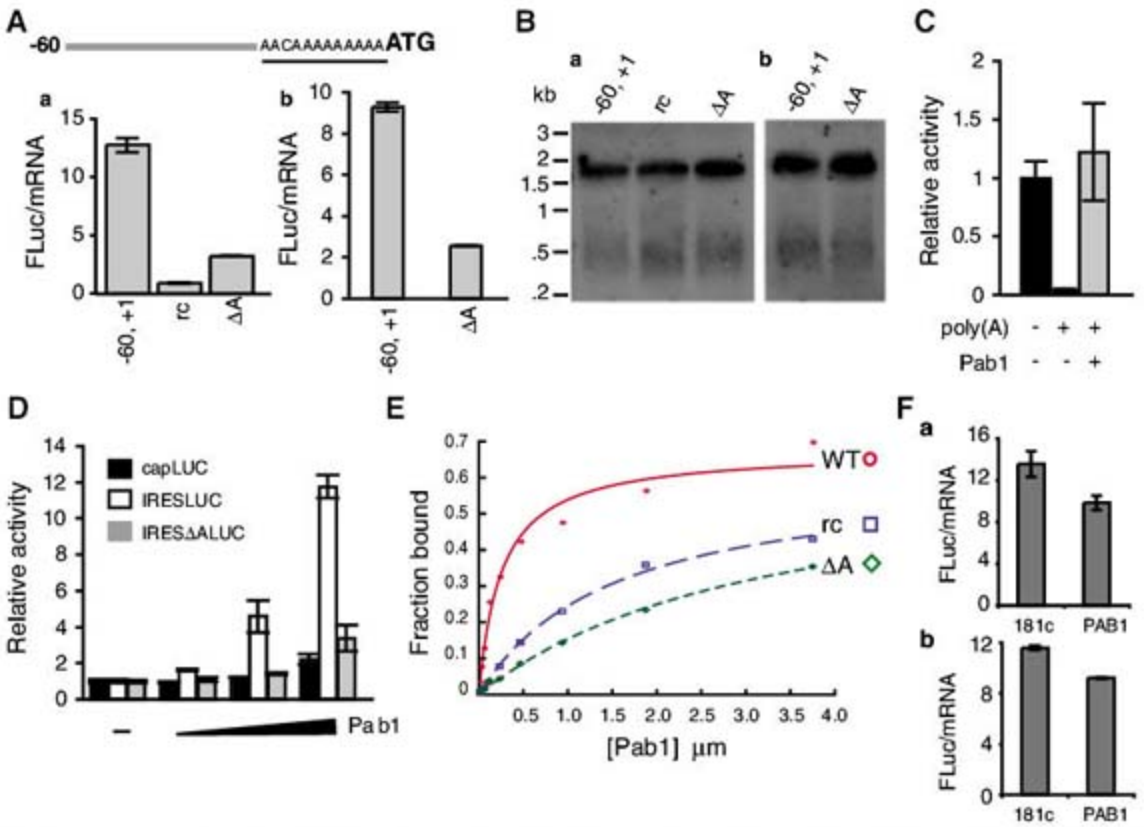

Fig. 3. An unstructured poly(A) tract mediates Pab1-dependent IRES activity. (**A**) Translation of ApppG-capped F-luc reporters containing *YMR181c* sequences or the reverse complement (rc) in yeast extracts (a) or cells (b) as described in Fig. 1. The 12-nt sequence deleted in ΔA is underlined. (**B**) Northern blots of F-luc mRNAs isolated from (A). (**C**) In vitro translation of ApppG-capped F-luc mRNA [lacking a poly(A) tail] ±100 ng exogenous poly(A) RNA ±100 ng of recombinant Pab1. The activity from the reaction without any additions was set equal to 1. Attempts to test the effects of Pab1 depletion using antibodies required high concentrations of antibody and prolonged incubations that resulted in nonspecific inactivation of extracts. (**D**) Translation of m7GpppG-capped (black), ApppG-capped + IRES (white) or ApppG-capped+IRESΔA (gray) F-luc mRNAs [lacking poly(A) tails] in the presence of 100, 200, or 400 ng rPab1 or buffer. Average activity from the reaction + buffer was set equal to 1 for each construct. (**E**) Filter-binding assay for binding of rPab1 to various *YMR181c* 5′UTR sequences showing the fraction bound for each concentration of rPab1. (**F**) Translation in vitro (a) and in vivo (b) of F-luc reporters containing 5′UTRs of *YMR181c* and *PAB1*, normalized to mRNA levels by Northern blot.

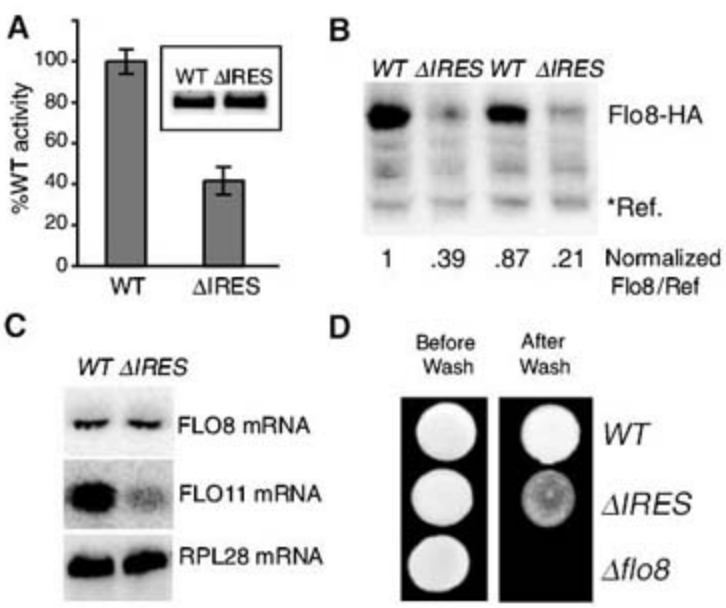

Fig. 4. IRES-dependent translation of FLO8 is required for invasive growth. (**A**) In vitro translation of ApppG-capped F-luc mRNAs containing the full-length 5′UTR from *FLO8* wild-type (WT) or a deletion mutant lacking nucleotides –60 to –11(Δ), normalized to mRNA levels by Northern blot (inset). (**B**) Western blot of Flo8 from two independent isolates each of WT *FLO8* or –60 to –11Δ mutant strains containing a C-terminal hemagglutinin (HA) epitope tag. The reference band (*Ref.) is a cross-reacting protein detected in untagged strains. Relative levels of Flo8-HA are indicated below. (**C**) Northern blots of RNA isolated from the extracts prepared in (B). (**D**) Invasive growth assay for WT, Δ*flo8*, and –60 to –11Δ strains. Portions of the cultures assayed in (B) and (C) were spotted onto rich medium and photographed after growth at 30°C. Invasive growth was photographed after washing the same plate under a gentle stream of water.

FLO11 (Fig. 4C). These data strongly argue for a physiological requirement for IRES-dependent translation in yeast invasive growth. Our findings demonstrate a direct connection between IRES activity and cellular differentiation and suggest a coherent molecular mechanism for internal initiation on cellular messages that may be conserved in higher eukaryotes.

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Strand-Biased Spreading of Mutations During Somatic Hypermutation

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Somatic hypermutation (SHM) is a major means by which diversity is achieved in antibody genes, and it is initiated by the deamination of cytosines to uracils in DNA by activation-induced deaminase (AID). However, the process that leads from these initiating deamination events to mutations at other residues remains poorly understood. We demonstrate that a single cytosine on the top (nontemplate) strand is sufficient to recruit AID and lead to mutations of upstream and downstream A/T residues. In contrast, the targeting of cytosines on the bottom strand by AID does not lead to substantial mutation of neighboring residues. This strand asymmetry is eliminated in mice deficient in mismatch repair, indicating that the error-prone mismatch repair machinery preferentially targets top-strand uracils in a way that promotes SHM during the antibody response.

During an immune response, B cells located in germinal centers of the lymph nodes and spleen mutate the variable region of their immunoglobulin (Ig) genes at high rates by the process of somatic hypermutation (SHM). SHM is critical for the generation of high-affinity antibodies and efficient immune responses (*1*). The reaction is initiated by the deamination of C to U in Ig genes by activation-induced deaminase (AID) (Fig. 1A) (*2*, *3*). These U's are detected either by uracil DNA glycosylase (UNG) and processed by the base excision repair pathway (*4*) or by the Msh2/Msh6 dimer and processed by the mismatch repair pathway (*5*–*11*) (Fig. 1A). Aberrant repair by these pathways in conjunction with error-prone polymerases (*12*), especially polymerase η (*13*–*16*), leads to a characteristic pattern of mutations (Fig. 1A) in which A residues are targeted approximately twice as frequently as T residues on the nontranscribed top strand (*17*). The origin of this asymmetry remains unknown. Furthermore, it has not been possible to link particular A/T mutations to the deamination of a defined C residue, leaving several central questions about SHM unanswered: (i) Do top- and bottom-strand deamination events lead to similar or different outcomes? (ii) Can a deamination event lead to A/T mutations upstream and downstream of it, or do mutations spread in only one direction? (iii) Over what distance can mutations spread from a single deamination event?

To address these issues, transgenic mice were generated with SHM substrates that contained a 100–base pair (bp) region devoid of or with only a single C residue at which the reaction could initiate (Fig. 1B) (*18*). Four variants of the parental Vκ167/PEPS Igκ transgene (*19*) were generated that differed only in a stretch of A/T nucleotides inserted near the 3′ end of the variable region (Fig. 1B): The transgene TgA contained five repeats of a 20-bp region consisting exclusively of A/T nucleotides, in a sequence chosen to maximize the occurrence of hotspots for SHM (*20*) (Fig. 1B and fig. S1). The transgene variant TgT contained the same 100 bp inserted in the reverse orientation. Because the entire 100-nucleotide (nt) stretch consisted of 50 A and 50 T residues, the overall sequence composition of TgA and TgT was identical. The transgenes TgG and TgC are identical to TgA and TgT, respectively, with the exception that they contain a single C:G (TgC) or G:C (TgG) base pair in the central repeat (Fig. 1B).

The copy number and expression level of the founder lines for each transgene showed large variation (*18*), leading us to select multiple lines of each transgene for further analysis (Table 1 and fig. S2). B cells were isolated from Peyer's patches of aged mice, and DNA was prepared from actively hypermutating germinal-center B cells ($B220^+CD19^+GL7^+$) and nonmutating control nongerminal-center B cells ($B220^+CD19^+GL7^-$). A 513-bp stretch encompassing most of the VJ region of the transgenic Ig gene, including the A/T tract, was analyzed for mutations (Figs. 1 and 2). 4.3 to 6.8% of the sequences from the $GL7^+$ samples were mutated (Table 1), with most mutated sequences possessing only a single mutation. Mutations observed in different lines of the same transgene showed similar patterns and were pooled and presented together (fig. S3 and table S1). The region outside of the A/T tract showed comparable mutations between the different constructs (Fig. 2A). We also sequenced the Ig heavy chain Jh4 intron from the same DNA samples to assess mutations in a region of the genome expected to be heavily mutated (*18*). B cells from mice harboring different transgenes had comparable levels of mutations in the Jh4 intron (fig. S4).

Analysis of the TgA and TgT lines showed that the mutation machinery was largely excluded from the A/T tract (Fig. 2B). The number of mutations was significantly lower than predicted by the mutability index of the region (P = 0.0002 and 0.0016 for TgA and TgT, respectively). The few mutations that were seen occurred in the peripheral portions of the A/T tract, up to 18 or 29 bp from the nearest C residue in the 5′ or 3′ flanks, respectively (Fig. 2B); thus, we presume that they arose from the deamination of C residues in the flanking regions. The complete protection of the central portion of the A/T tract in TgA

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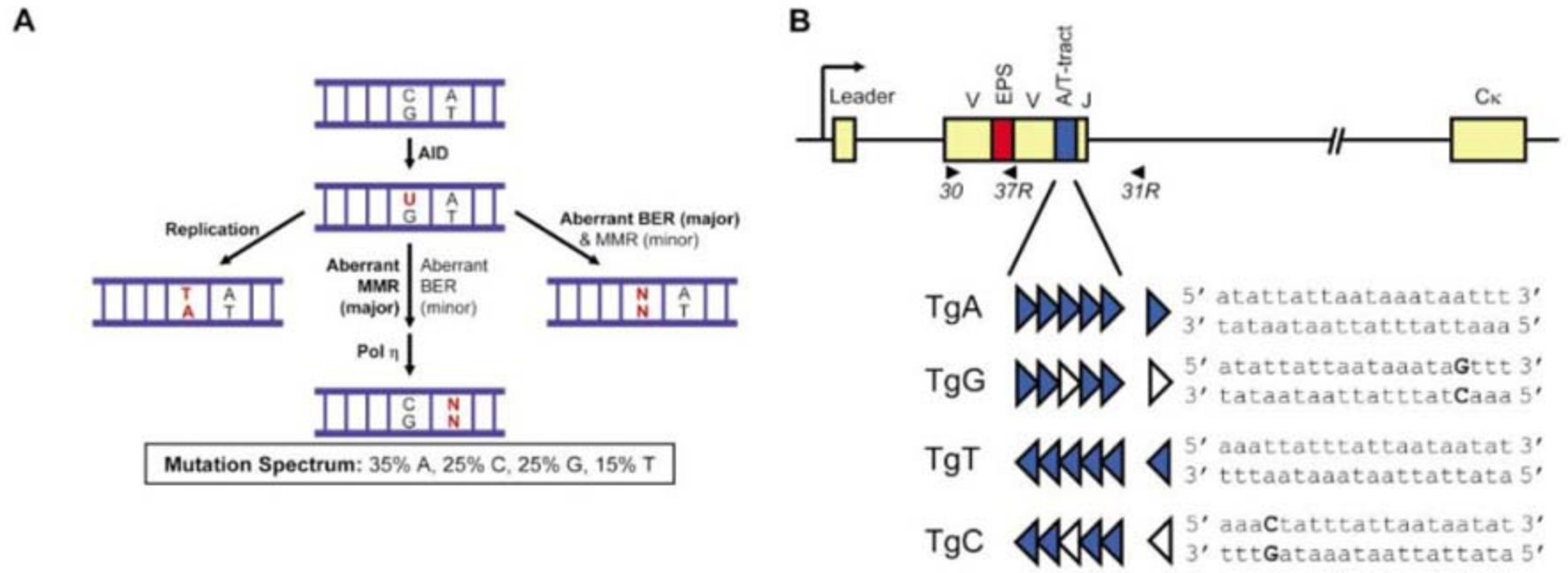

Fig. 1. (**A**) Mutation pathways in somatic hypermutation. The schematic is based on models proposed by Di Noia *et al.* (*3*). Base alterations are shown in red. MMR, mismatch repair; BER, base excision repair; Pol, polymerase. (**B**) Transgenes used in the study. The parental Igκ transgene Vκ167/PEPS (≈14 kb) includes the VJ region and promoter (arrow); the constant region (Cκ); the Igκ intronic and 3′ enhancer elements (not shown); and an EPS cassette, which is a mutation-prone repetitive sequence (*19*). The A/T inserts in TgA and TgT contain five repeats of a 20-bp A/T sequence (blue triangles). Transgenes TgG and TgC are identical to TgA and TgT, respectively, but have a single C:G (TgC) or G:C base pair (TgG) in the central repeat (white triangles). Primers PEPS30 and PEPS37R were used for reverse transcription polymerase chain reaction (RT-PCR), and primers PEPS30 and PEPS31R were used to amplify a 706-bp region, of which a central 513-bp region was sequenced.

Table 1. Summary of mutation data. The PCR error rate was 2.9×10^{-6} mutations per base pair. n.d., not done.

Parameter	TgA	TgC		TgG		TgT
	WT	WT	Msh2$^{-/-}$	WT	Msh2$^{-/-}$	WT
Number of lines examined*	6	5	2	4	2	4
Copy number	1–3	6–>63	6–>63	2–14	2–14	3–12
Expression per copy†	3.4–192.8	1.6–22.4	1.6–22.4	0.6–16.4	0.6–16.4	4.0–36.4
Mutation frequency of GL7$^+$ (mutations/base pair)	1.5×10^{-4}	1.1×10^{-4}	3.0×10^{-5}	1.0×10^{-4}	2.7×10^{-5}	1.1×10^{-4}
Mutation frequency of GL7$^-$‡ (mutations/base pair)	0	0	n.d.	0	n.d.	0
Frequency of mutated sequences of GL7$^+$ (%)	6.8	5.1	1.5	4.3	1.3	5.2
Frequency of mutated sequences of GL7$^-$‡ (%)	0.0	0.0	n.d.	0.0	n.d.	0.0

*Number of different founder lines from which mutation data were collected. †Range of expression of the transgene in the lines analyzed for mutations measured by quantitative RT-PCR and normalized to the expression of the RSA transgene (*23*) and the copy number of each transgenic line. The expression of mb1 was used as an internal control (fig. S2). ‡More than 250 sequences for each construct.

and TgT strongly suggests that the mutation of A and T residues requires the presence of a C/G base pair nearby.

In agreement with such a mechanism, TgC accumulated a significant number of mutations in the A/T tract (Fig. 2B), demonstrating that a single C residue on the top strand is sufficient to initiate mutations at nearby A/T residues. However, TgG showed very few mutations in the A/T tract, yielding a mutation pattern much more similar to that of the constructs lacking the central C residue. The only mutation in the A/T tract near the G:C base pair of TgG was located 12 bp away (Fig. 2B), and it was not obvious whether this occurred as a consequence of targeting of the central C on the bottom strand or because of the deamination of a C residue 32 bp away in the downstream flank (Fig. 2B). The results from TgG suggest that a C on the bottom strand had little or no ability to direct mutations to nearby A/T residues. This was not due to the failure of deamination of the C on the bottom strand, because at least two independent mutations (from different transgenic lines) occurred at this residue (Fig. 2B). We conclude that although top- and bottom-strand C residues are both targets of AID, they support distinct outcomes during SHM. Thus, a top-strand C allows the spread of mutations to nearby A/T residues, whereas a bottom-strand C does so poorly or not at all.

The pattern of mutations in these transgenes reveals novel information about how mutations at A/T residues arise from a deaminated C during SHM. Mutations accumulated on both sides of the central C residue in TgC. Particularly striking are clusters of mutations 9 to 15 bp upstream and 4 to 10 bp downstream of the C, regions that are never mutated in TgA or TgT. This strongly suggests that the error-prone gap repair initiated by the deamination of C can extend to both the 5′ and 3′ sides of the U. This is further supported by the observation that the A/T tract in TgA and TgT accumulated mutations near both flanks. The results also provide insight into how far mutations can spread during SHM, revealing that the gap of error-prone repair can extend at least 18 nt downstream and 29 nt upstream of an initiating C-deamination event. This might reflect the size of the gap created during normal (error-free) mismatch repair, a parameter not previously measured in vivo.

The different outcomes we observed with top- and bottom-strand C residues could arise from asymmetric targeting of either AID or subsequent repair steps. In mice deficient in both

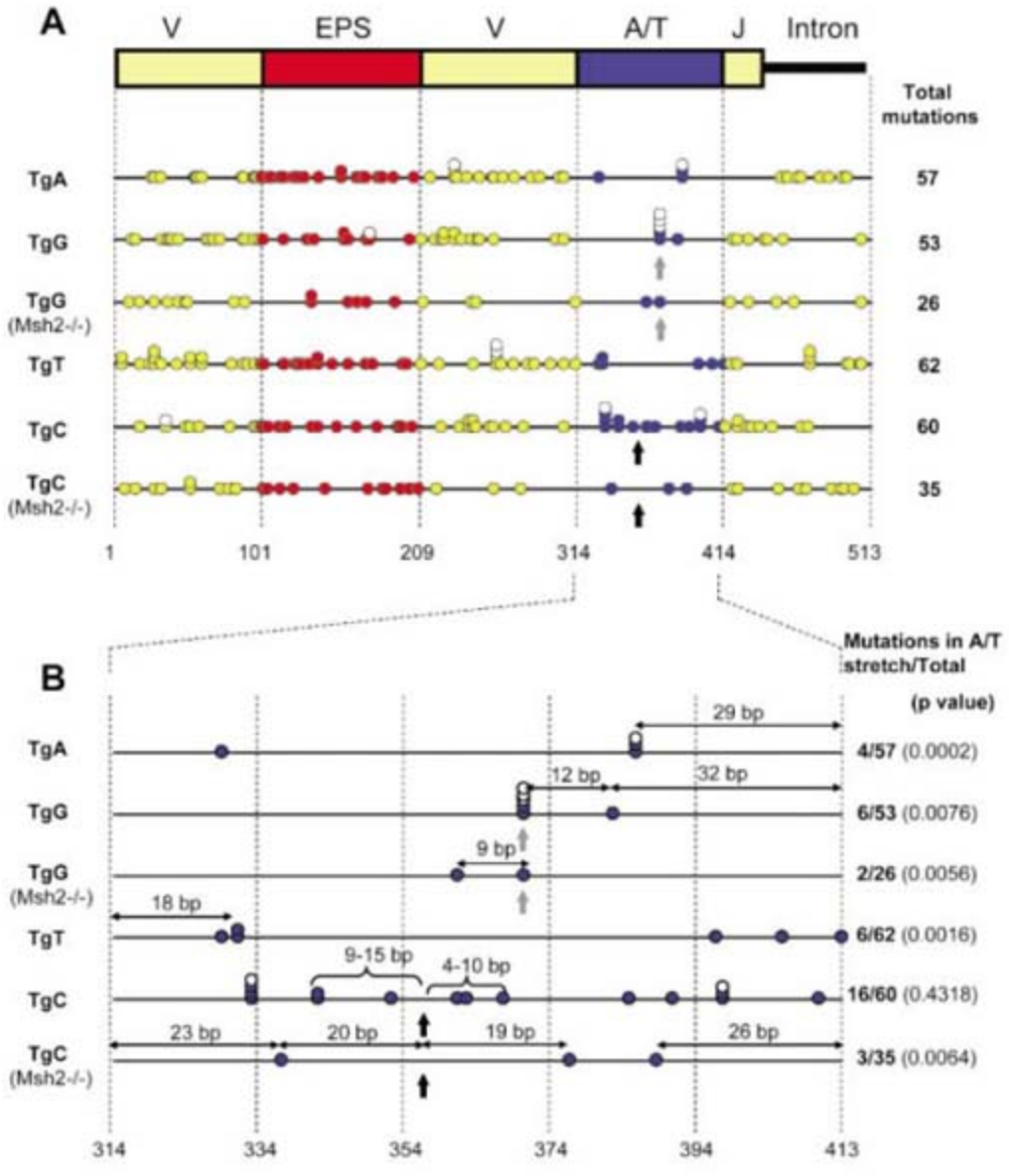

Fig. 2. Distribution of mutations. (**A**) Summary of all mutations. The 513-bp region analyzed was divided into five subregions, as indicated. Individual mutations are shown as solid circles (independent mutations) or open circles (identical mutations obtained from independent amplifications of the same substrate DNA, which are potentially clonally related to a solid-circle mutation). TgC and TgG from Msh2$^{-/-}$ mice were also analyzed, as indicated at left. The total number of mutations obtained in each transgene is shown at right. The positions of the central G:C (TgG, gray arrows) and C:G (TgC, black arrows) base pairs are shown. (**B**) Mutations in the A/T tract. The numbers at right denote the number of mutations in the A/T tract divided by the total number of mutations. The numbers in parentheses are the two-tailed *P* values for the fraction of mutations in the A/T tract (*18*). The distances of selected mutations from the nearest top-strand C residue are indicated.

UNG and Msh2, which cannot repair AID-generated U's, C and G mutate at equal frequency, suggesting that AID deaminates the top and bottom strands equally (*21*, *22*). However, it is possible that in the specific context of the central C of TgC and TgG, AID is asymmetric in its action. Alternatively, because most A/T mutations result from mismatch repair (*5*, *6*), strand-asymmetric mismatch repair could lead to the observed asymmetry. According to this model, top-strand U's initiate error-prone gap repair and mutation of A/T residues in a process involving Msh2/6, Exo1, and polymerase η (and perhaps other error-prone polymerases), whereas bottom-strand U's are repaired by a distinct mechanism that is less error-prone. If top-strand U's lead to gap repair preferentially (or exclusively) on the top strand, then this model, together with the strong propensity of polymerase η to misincorporate opposite template T, provides an explanation for the A > T strand bias of SHM.

A key prediction of this model is that the mutational asymmetry between TgC and TgG should be eliminated in mismatch repair–deficient mice. To test this idea, we crossed two lines each of TgC and TgG mice onto the Msh2$^{-/-}$ background and assessed transgene mutation as before (Fig. 2, fig. S5, and table S2). As observed in previous studies, Msh2$^{-/-}$ mice showed a three- to four-fold decrease in mutation frequency as compared with wild-type (WT) mice (Table 1). Analysis of TgC revealed that although regions outside the A/T tract continued to mutate in the absence of Msh2, the accumulation of mutations within the A/T tract was substantially reduced [3 out of 35 (3/35) in Msh2$^{-/-}$ versus 16/60 in the wild type] to a level well below that expected on the basis of the mutability index of the region ($P = 0.0064$) (Fig. 2). The residual level of A/T tract mutation in TgC was comparable to the level seen in TgG, both in WT (6/53) and Msh2$^{-/-}$ mice (2/26). These results support the hypothesis that the strand-biased spread of mutations in SHM arises from preferential targeting of the error-prone mismatch repair pathway to top-strand (as compared with bottom-strand) U's. In addition, the data are most easily explained by the idea that AID accesses both strands equally and that, in the absence of Msh2, the resulting U's are processed by a UNG-dependent pathway in a strand-unbiased manner. Hence, in WT mice, the base excision repair pathway would be predicted to account for a small fraction of mutation spreading on the top strand and for most or all of the spreading on the bottom strand. Like mismatch repair, base excision repair also appears to spread mutations over a long distance (20 bases upstream and 26 bases downstream).

The present study demonstrates the absolute dependence of SHM on C residues and reveals important parameters, including distance and direction, of the process by which mutations spread from a C to nearby A/T residues. In addition, the results reveal an asymmetry in the targeting of mismatch repair, but not base excision repair, to lesions on the top versus bottom strand, resulting in differential repair of the two strands.

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Localization of a Stable Neural Correlate of Associative Memory

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Do learning and retrieval of a memory activate the same neurons? Does the number of reactivated neurons correlate with memory strength? We developed a transgenic mouse that enables the long-lasting genetic tagging of c-*fos*–active neurons. We found neurons in the basolateral amygdala that are activated during Pavlovian fear conditioning and are reactivated during memory retrieval. The number of reactivated neurons correlated positively with the behavioral expression of the fear memory, indicating a stable neural correlate of associative memory. The ability to manipulate these neurons genetically should allow a more precise dissection of the molecular mechanisms of memory encoding within a distributed neuronal network.

Memories are presumably stored in subgroups of neurons that are activated in response to a given conjunction of sensory inputs. Sparse encoding of memories in complex neuronal networks has been identified with electrophysiological recordings of large groups of single units (*1*–*4*). Similar approaches have identified neurons with firing properties temporally linked to various aspects of task performance (*5*), and imaging techniques have enabled the physical localization of neurons that are activated during either learning or retrieval of a memory (*6*–*9*). In an associative task, the sensory stimuli and their temporal relationships differ during the learning and retrieval trial, and it is unclear to what extent the neuronal representations of these two events overlap.

We generated a transgenic mouse (TetTag mouse) that allows the persistent tagging of neurons that are activated during a given time window (Fig. 1A). The tag can be used for the direct comparison of neuronal ensemble activity at two widely spaced time points. The TetTag mouse combines elements of the tetracycline-transactivator (tTA) system for transgene regulation with neuronal activity–induced activation of the c-fos promoter to tag activated neurons (*10*–*13*). We used seizure-induced neuronal activation to test various aspects of regulation in the TetTag mouse. As shown in Fig. 1B, tau-LacZ (LAC) expression had a low baseline, could be induced broadly in the brain by seizure in a doxycycline (Dox)–regulated manner (figs. S1 and S2), and could be maintained for at least 5 days in the presence of Dox after the initial activation.

The TetTag mouse was used to determine whether neurons that are activated during learning are reactivated during retrieval. We used expression of LAC as an indicator of neuronal activity during learning and expression of the immediate-early gene *Zif/Egr* (ZIF) as an indicator of neuronal activity during retrieval (Fig. 2A) (*6*, *7*, *9*). We assessed associative memory using fear conditioning, with a focus on the learning and retrieval of a context-shock association (*14*, *15*). The basolateral amygdala (BLA) has been implicated as a potential storage site for context-shock associations (*16*–*18*). Using the

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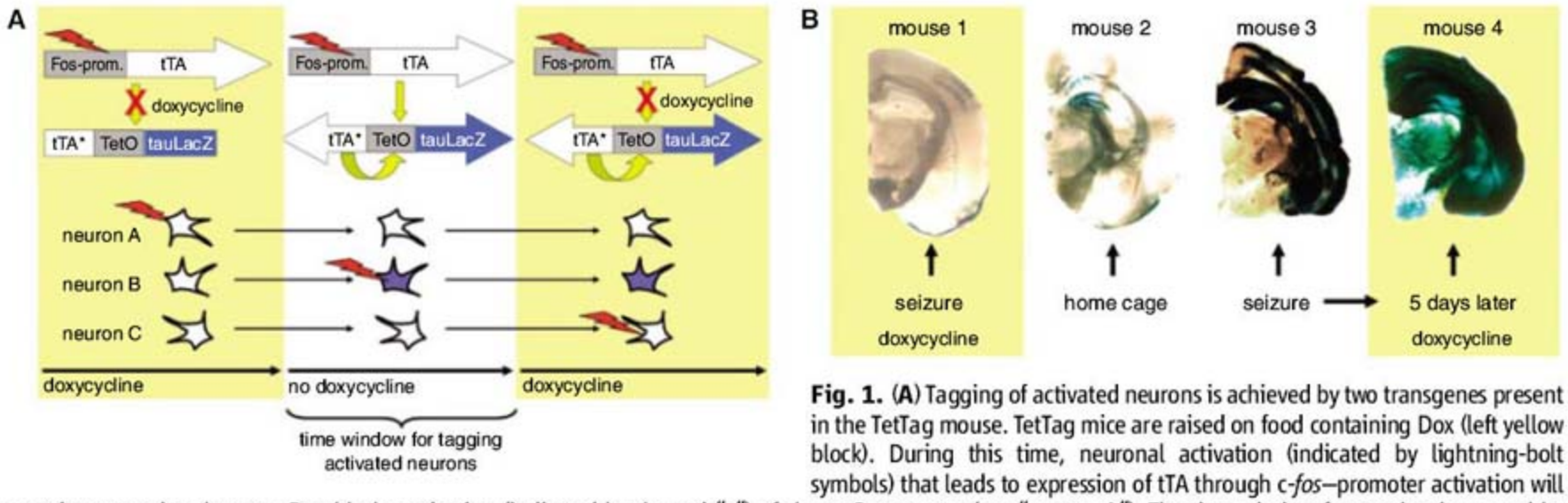


Fig. 1. (**A**) Tagging of activated neurons is achieved by two transgenes present in the TetTag mouse. TetTag mice are raised on food containing Dox (left yellow block). During this time, neuronal activation (indicated by lightning-bolt symbols) that leads to expression of tTA through c-*fos*–promoter activation will not trigger tagging, because Dox blocks activation (indicated by the red "x") of the tetO promoter (see "neuron A"). The time window for tagging is opened by switching mice to food without Dox (middle white block). Neuronal activation will now activate the transcriptional feedback loop and start expression of tau-LacZ (see "neuron B"). The time window is closed by putting mice back on Dox food (right yellow block) to block further feedback loop activation (see "neuron C"). However, neurons that were activated during the "no Dox" time window will continue to express tau-LacZ (see neuron B), because the feedback loop can maintain its own activation through the Dox-insensitive tTA^{H100Y} (tTA*), where H100Y represents His^{100}→Tyr^{100}. (**B**) Kainic acid–induced seizures were used to test whether Dox can be used to open a time window for tagging activated neurons. In the presence of Dox, no neurons are tagged after induction of seizure, as indicated by X-Gal (5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside) staining of a coronal section ("mouse 1"). When a TetTag mouse is left in the home cage in the absence of Dox, only a limited number of neurons are tagged ("mouse 2"). Seizure in the absence of Dox triggers the tagging of a large number of neurons throughout the forebrain, as can be seen at 7 hours ("mouse 3") and 5 days ("mouse 4") after seizure. "Mouse 4" was put on Dox food immediately after seizure.

TetTag mice, we were able to identify neurons in the BLA that express both LAC and ZIF after learning and retrieval of conditioned fear (Fig. 2B). These reactivated neurons are probably projection neurons, because LAC neurons in the BLA did not overlap with γ-aminobutyric acid–containing neurons (fig. S3).

The experiment, outlined in Fig. 3A, used four groups of mice: The home cage (HC) group remained in the home cage throughout the experiment, the fear-conditioning (FC) group underwent fear-conditioning training and was tested for retrieval 3 days later, the fear-conditioning no-retrieval (FC-NR) group was not subjected to a retrieval test, and the no-shock (NS) group was treated identically to the FC group except that no shocks were administered. The FC group had higher freezing (lack of complete movement) scores during context retrieval than the NS group (Fig. 3B). BLA neurons activated during learning of conditioned fear were tagged, as was shown by the higher number of LAC-positive neurons in the combined FC groups as compared with those in both the HC and NS groups (Fig. 3C). This increase in LAC was not caused by retrieval-induced activation, because there was no difference between the FC and FC-NR groups [$t(16) = 0.77$]. We next asked whether neurons activated during fear conditioning were reactivated during retrieval. No significant differences in the number of ZIF neurons were found ($F_{2,29} = 0.28$); however, the FC group had a higher number of LAC+ZIF–positive neurons than the HC and NS groups (Fig. 3D). Only the FC group showed overlapping expression that was significantly higher than expected by chance (Fig. 3D). After normalizing for chance overlap, the FC group had more LAC+ZIF neurons than the HC and FC-NR groups (Fig. 3E).

Does the strength of neuronal reactivation in the BLA correlate with the strength of the memory retrieval? We used extinction to weaken the expression of the fear memory (*19*). Two groups of mice were used: The FC group was treated identically to the FC group from the previous experiment, whereas the extinction (EX) group was subjected to extinction trials between learning and retrieval (Fig. 4A). Extinc-

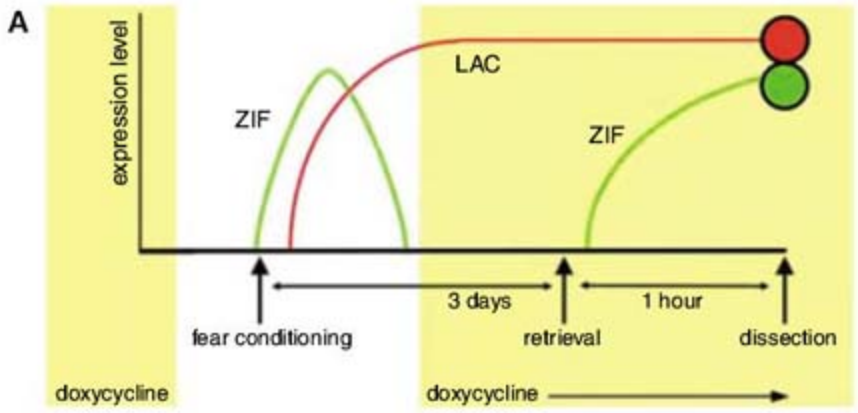
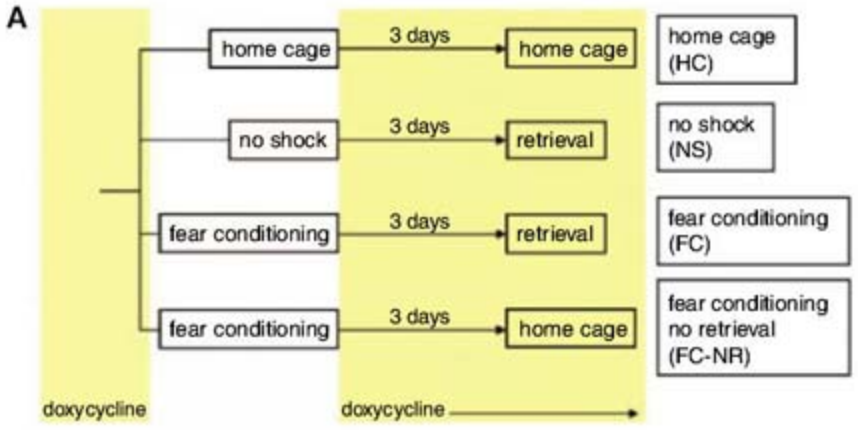


Fig. 2. (**A**) A protocol was designed to detect repeated activation of neurons during learning and retrieval of conditioned fear. Learning takes place in the absence of Dox, when activation of neurons triggers long-lasting expression of LAC and short-lasting expression of immediate-early genes like *Zif/Egr* (ZIF). Retrieval takes place 3 days after learning in the presence of Dox, which prevents activation of the molecular feedback loop. Dissection of brains is done 1 hour after retrieval, when LAC and ZIF can be used as indicators of learning-induced and retrieval-induced activation, respectively. (**B**) Example of LAC and ZIF expression in BLA neurons of a mouse that was subjected to the protocol described in (A). The yellow square in the left darkfield picture marks the area shown in the three immunostaining pictures. Yellow arrows mark neurons that express both LAC and ZIF. Scale bar, 100 μm. CA, central amygdala.



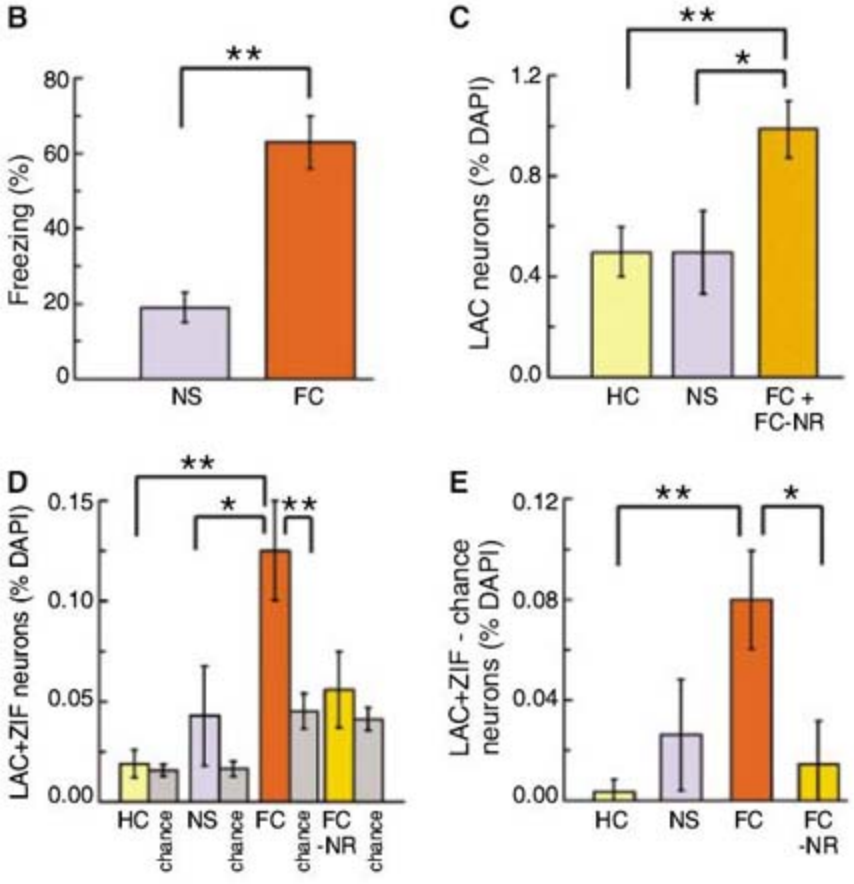


Fig. 3. Reactivated neurons in the BLA during fear conditioning provide a stable neural correlate of associative memory. (**A**) Diagram of the experimental design. HC, $n = 21$ mice; NS, $n = 10$ mice; FC, $n = 10$ mice; FC-NR, $n = 8$ mice. (**B**) The FC group showed more freezing than the NS group during context retrieval [$t(18) = 5.9$, $P = 0.00001$]. (**C**) The combined FC and FC-NR group had an increased number of LAC-positive neurons as compared with both the HC and NS groups ($F_{2,46} = 6.2$, $P = 0.004$). (**D**) The FC group had a higher number of LAC+ZIF–positive neurons than the HC and NS groups ($F_{3,45} = 7.7$, $P = 0.0003$). In the FC group, but not the other three groups, the number of LAC+ZIF neurons was higher than chance level [FC: $t(9) = 4.1$, $P = 0.003$]. (**E**) The FC group had more LAC+ZIF neurons than the HC and FC-NR groups after subtracting chance level ($F_{3,45} = 5.7$, $P = 0.002$). Data in (C) to (E) are percentages of total neurons as determined by 4′,6′-diamidino-2-phenylindole (DAPI) staining. Means ± SEM are shown in (B) to (E). *$P < 0.05$, **$P < 0.01$.

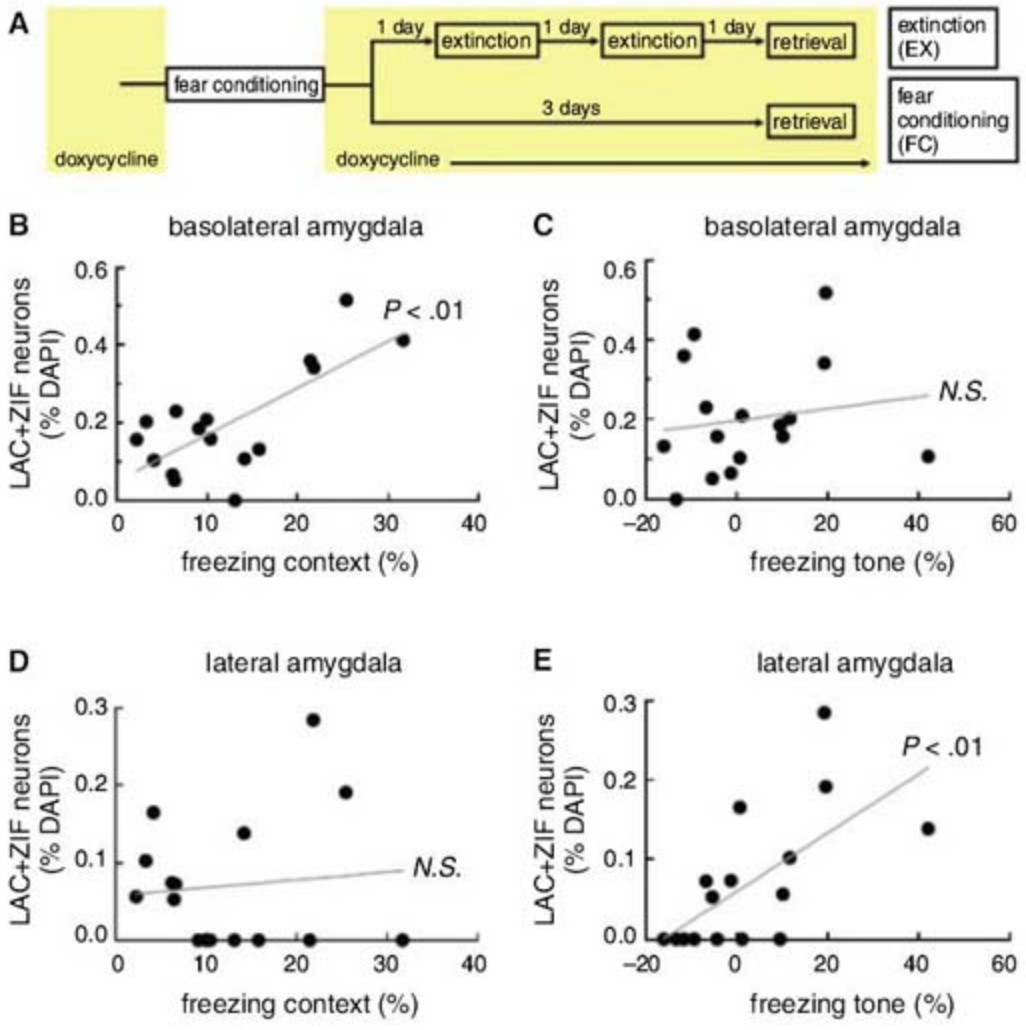


Fig. 4. The number of reactivated neurons in the BLA and LA correlates with the strength of the conditioned fear memory. (**A**) Diagram of the experimental design. EX, $n = 16$ mice; FC, $n = 6$ mice. (**B**) Within the EX group, the number of LAC+ZIF neurons in the BLA correlated with freezing during context retrieval ($R = 0.73$, $P = 0.001$). (**C**) The number of BLA LAC+ZIF neurons did not correlate with the estimated freezing during tone retrieval ($R = 0.16$, $P = 0.6$). N.S., not significant. Freezing during tone retrieval was estimated by subtracting the freezing before the first tone from the freezing during the first tone. (**D**) In the LA, the number of LAC+ZIF neurons did not correlate with freezing during context retrieval ($R = 0.10$, $P = 0.7$). (**E**) In the LA, there was a significant correlation between the number of LAC+ZIF neurons and the estimated freezing during tone retrieval ($R = 0.65$, $P = 0.006$).

tion resulted in a significant decrease in fear-memory expression, as indicated by freezing during context retrieval [EX: 13 ± 2% freezing due to context retrieval; FC: 53 ± 9%; $t(20) = 6.4$, $P = 0.000003$]. The EX and FC groups had similar numbers of LAC, ZIF, or LAC+ZIF neurons in the BLA ($F_{1,20} = 0.00$, $F_{1,20} = 0.34$, and $F_{1,20} = 0.61$, respectively). However, extinction showed variable effectiveness in individual mice, with freezing scores ranging from 2 to 32%. This result allowed us to look for a correlation, within a group of similarly treated mice, between the strength of (behaviorally expressed) conditioned fear and the number of reactivated neurons. Within the EX group, there was a strong correlation between the number of LAC+ZIF neurons and the freezing score measured during context retrieval (Fig. 4B). There was no correlation with LAC alone ($R = 0.26$, $P = 0.3$) or ZIF alone ($R = 0.23$, $P = 0.4$). Training, extinction, and retrieval used both the context and a tone as conditioned stimuli (CS) so that neuronal correlates of both memories could be examined. Freezing scores shown in Fig. 4B were obtained during the beginning of the retrieval test before the first tone and thus indicated contextual fear memory. We obtained an estimate of the strength of the tone fear memory by subtracting the freezing before the first tone from the freezing during the first tone. There was no correlation between the estimated freezing during tone retrieval and the number of reactivated neurons in the BLA (Fig. 4C). However, the number of reactivated neurons in the lateral amygdala (LA) correlated with the estimated freezing during tone retrieval but did not correlate with the freezing during context retrieval (Fig. 4, D and E).

We localized a group of neurons in the amygdala that was activated during learning and reactivated during retrieval of a fear memory. Reactivation of neurons in the BLA and LA correlated with contextual and tone fear memory, respectively, which is in accordance with previous studies (*17*, *18*). The reactivated neurons did not simply respond to the repeated pattern of CS (i.e., context and tone), because the unconditioned stimulus (US) (i.e., shock) was required during learning-induced activation but not during retrieval-induced reactivation. Hebbian models of plasticity postulate that synaptic weight changes should occur at synapses that are active concurrently with neuronal firing. In fear conditioning, this should occur at neurons that receive both CS and US inputs, such that the enhanced strength of the CS inputs produced by Hebbian plasticity would allow firing (or increased rates of firing) of conditioning-activated neurons in response to the CS presentation alone during the retrieval trial. This reactivation would, in effect, recapitulate aspects of the original learning episode. In the FC group, 12% of the neurons tagged with LAC were reactivated during retrieval (Fig. 3, C and D). The nonreactivated LAC cells would represent either neurons activated in the home cage (as observed in the HC group in Fig. 3C) or US-stimulated neurons that did not receive CS inputs during learning and were therefore not reactivated during retrieval. Previous studies found neurons in the BLA and LA that receive convergent projections from CS and US pathways and that can undergo fear conditioning–induced Hebbian plasticity that lasts for several hours (*4*, *16*, *20*, *21*). The current result suggests that this plasticity evolves into stable synaptic changes that confer on these neurons a capacity for reactivation by the CS that lasts for at least 3 days. The reactivated neurons seem to be a likely component of a stable engram or memory trace for conditioned fear.

The TetTag mouse provides a distinctive tool for localizing memories in a complex neuronal network. It combines the ability to image all the neurons in the region of interest with the ability to assess activation of the same neuron at widely separate time points. Because reactivation of neurons takes place in freely moving mice, it can be correlated with the behavioral expression of the memory. Use of the TetTag mouse only requires basic immunohistochemistry and microscopy tools, which are available to most researchers. The TetTag mouse not only provides a tag through the expression of a reporter gene, but can also drive the expression of additional transgenes that can be used to both follow and manipulate the physiology of the tagged neurons (*22*).

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Supporting Online Material
www.sciencemag.org/cgi/content/full/317/5842/1230/DC1
Materials and Methods
Figs. S1 to S3
References

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Land-Use Allocation Protects the Peruvian Amazon

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Disturbance and deforestation have profound ecological and socioeconomic effects on tropical forests, but their diffuse patterns are difficult to detect and quantify at regional scales. We expanded the Carnegie forest damage detection system to show that, between 1999 and 2005, disturbance and deforestation rates throughout the Peruvian Amazon averaged 632 square kilometers per year and 645 square kilometers per year, respectively. However, only 1 to 2% occurred within natural protected areas, indigenous territories contained only 11% of the forest disturbances and 9% of the deforestation, and recent forest concessions effectively protected against clear-cutting. Although the region shows recent increases in disturbance and deforestation rates and leakage into forests surrounding concession areas, land-use policy and remoteness are serving to protect the Peruvian Amazon.

Tropical forests play essential roles in ecological, climate, and biogeochemical processes and in the lives of human populations (*1*–*4*), but anthropogenic disturbances can disrupt forest structure, function, and composition (*5*–*7*). Because of its large, relatively contiguous area of primary rainforest, the Peruvian Amazon has major conservation value and is considered a priority in nearly all global biodiversity inventories (*8*). Despite the internationally recognized uniqueness and importance of Peruvian rainforest ecosystems, the impacts of human activities throughout the region remain poorly understood.

Increasing rates of large-scale forest damage in the neighboring Brazilian Amazon have been linked to modern road building and government policies supporting resource extraction and settlement (*9*, *10*). Peru's 661,000 km^2 of Amazon tropical forest are also subject to elevated human impacts that have not been well documented at the landscape level: The paving of the Inter-Oceanic Highway and the spreading road network throughout the Pucallpa region have brought migrants mostly from the Peruvian Andes, along with largely undocumented impacts on forest cover and structure. However, in recent years the Peruvian government has also established or extended large natural protected areas and indigenous territories in the Peruvian Amazon, and forest management legislation has placed 31% of its forests into permanent resource production status (table S9), 104,970 km^2 of which went into long-term, timber-producing, commercial concessions by 2005 (*11*). Small-scale studies have noted an increase in forest damage within some protected areas, mostly as a result of land conversion to agriculture and pasture near human settlements and river valleys (*12*) associated with proximity to roads, rural credit programs, and access to markets (*13*), as well as inadequate land-use planning and governance (*14*). However, a synoptic assessment of forest disturbance and deforestation has not been derived for Peruvian forests.

Large-scale assessments of forest disturbance in the Peruvian Amazon, typically diffuse and difficult to detect, require complex detection algorithms for the analysis of high-resolution satellite imagery (*15*, *16*), but these methods are just now proving critical for land management, conservation analysis, and land-use policy assessments in tropical forest regions (*17*). We adapted a satellite-based forest disturbance detection system, originally designed for industrial-grade timber extraction monitoring in Brazil, to Peru's generally smaller-scale forest disturbance regimes. We present an updated version of the Carnegie Landsat Analysis System (CLAS, http://asnerlab.stanford.edu) and applied it to a study area covering 79% of the Peruvian Amazon (*18*) from 1999 to 2005. The core technology of the CLAS change-detection algorithm (*15*, *19*, *20*) was improved with optimized, automated versions of the atmospheric and haze correction and the water- and/or cloud-masking processes of the Monte Carlo unmixing (AutoMCU) approach (*21*). We also added an automated deforestation-detection component to provide an integrated analysis of both diffuse forest disturbance and clear-cutting. We used 101 Landsat 5 TM (Thematic Mapper) and Landsat 7 ETM+ (Enhanced Thematic Mapper Plus) satellite images at a spatial resolution of 30 m by 30 m to derive annual incremental damage maps for most of the human-impacted, timber-producing regions—up to 24 images per year, with each nonoverlapping footprint covering 26,000 km^2. The satellite detection results were validated via a large field survey in the Pachitea and Ucayali watershed regions and regionally evaluated against available land use, land cover, and conservation maps.

We found that 632 ± 230 km^2 year^{-1} and 645 ± 325 km^2 year^{-1} of Peruvian Amazon forests were subjected to new forest disturbances and

Table 1. Forest disturbance and deforestation area estimates for Peruvian Amazon tropical forest based on CLAS methodology. The number of satellite paths per rows in each year varied according to image availability. There were 23 path/row in 1999–2000, 23 in 2000–01, and 17 in 2001–02. On the basis of an assessment of the spatial distribution of forest damage in the first 3 years, a subset of satellite path/row was selected for analyses in the following 3 years, as available: 5 path/row in 2000–03, 3 in 2003–04, and 5 in 2004–05.

Year	Damage rates (km^{-2} year^{-1})	
	Disturbed	Deforested
1999–2000	653	731
2000–2001	617	698
2001–2002	508	616
2002–2003	409	470
2003–2004	546	192
2004–2005	1070	1174
Mean	634	647

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deforestation, respectively, between 1999 and 2005 (Fig. 1 and Table 1). Our forest disturbance values represent previously unaccounted human impacts throughout the region. The deforestation portion of our analysis is in agreement with Food and Agriculture Organization (FAO) deforestation estimates (table S1) but are lower than those reported by the Peruvian government (*21*–*23*).

Between 1999 and 2001, we found that 86% of all forest damage was concentrated in only two regions. In this period, the four satellite scenes covering the area around the Ucayali logging center of Pucallpa, and along the road network that emanates from it (Fig. 2), had the highest rates of forest disturbance and deforestation, contributing 64% of the total Peruvian Amazon damage. This was followed by the four satellite images covering the corridor centered in the eastern Madre de Dios capital city of Puerto Maldonado, which extended along the Inter-Oceanic Highway, showing 23% of the total damage (Fig. 1). We therefore concentrated on a five-satellite-scene subset for more detailed analyses from 1999 to 2005. Within this subset, forest damage rates remained relatively constant between 1999 and 2003, with average forest disturbances and deforestation rates of 340 ± 44 km^2 year^{-1} and 469 ± 35 km^2 year^{-1}, respectively (table S7). Total forest damage rates then increased substantially between 2003 and 2005, particularly in the last year of our analysis, when disturbance and deforestation rates of 995 km^2 year^{-1} and 1140 km^2 year^{-1} were 2.9 and 2.4 times higher than the average for the initial 4 years, respectively (*21*). In particular, forest disturbance greatly increased east of Pucallpa in 2004 and west of the Iberia area of Madre de Dios in 2005, in regions where forest concessions had recently been granted.

Forest disturbances and deforestation were detected in other areas to the north near the Loreto capital of Iquitos, where early indications of small-scale damage were seen in 1999, but these increased in intensity over the years of analysis, spreading to nearby forest areas on both sides of the Amazon River (Fig. 1). The northern Loreto forests close to the Colombian border, which maintained relatively low damage rates between 1999 and 2002, mostly in and around native communities' lands along rivers, showed only a slight increase in forest disturbances by 2004–05. The remote Napo moist forests of western Loreto showed very little damage between 1999 and 2002, which was concentrated on river edges (*17*). The concentration of forest damage along the Iquitos-to-Nauta road is a clear indication that road access could be the most important control over forest disturbance and deforestation rates in the remote Peruvian Amazon, where sheer distance and the intricate hydrologic network of the Amazon and Marañón rivers likely prevent high damage intensities and where timber extraction may be limited by current road access to markets (*9*).

Overall, only 2% of the forest disturbances and 1% of the deforestation detected in the entire study area occurred within the boundaries of natural protected areas. Furthermore, territories occupied by indigenous communities contained 11% and 9% of the total forest disturbance and deforestation, respectively (Table 2). These results show that these two forms of land-use allocation can provide effective protection against forest damage. However, a few exceptions occurring on indigenous community lands in the Oxapampa and Puerto Inca provinces and, to a lesser extent, in the El Sira natural protected area

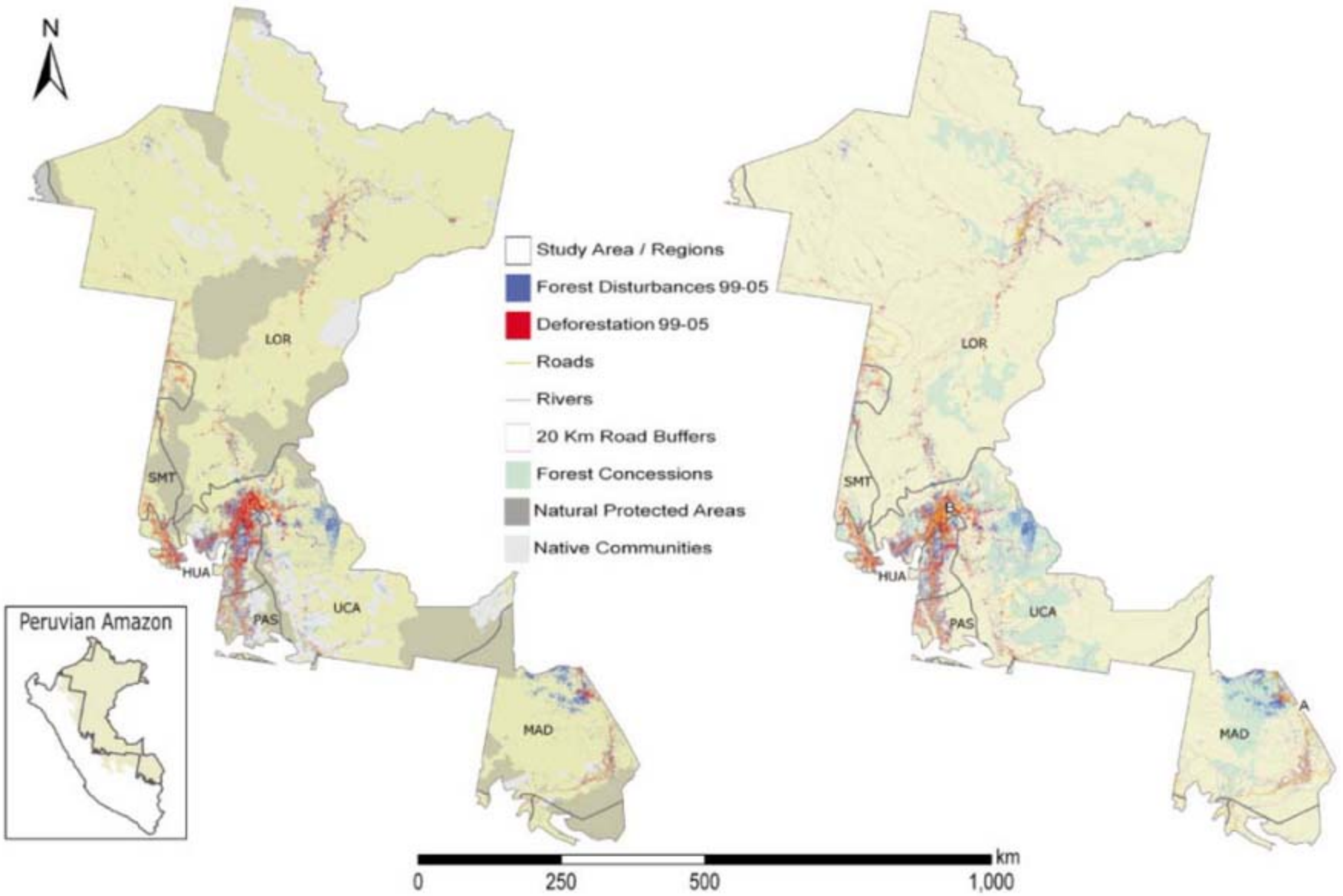

Fig. 1. Cumulative spatial distribution of forest disturbance (blue) and deforestation (red) in the Peruvian Amazon between 1999 and 2005. (**Left**) Light gray areas show the extent of native territories, and dark gray areas show natural protected areas. (**Right**) Orange lines show road distribution, magenta lines shows 20-km road buffers, and green areas show the extent of forest concessions allocated by 2005; letters A and B denote the Pucallpa and Inter-Oceanic Highway regions, respectively. LOR indicates Loreto; SMT, San Martín; HUA, Huánuco; PAS, PASCO; UCA, Ucayali; and MAD, Madre de Dios.

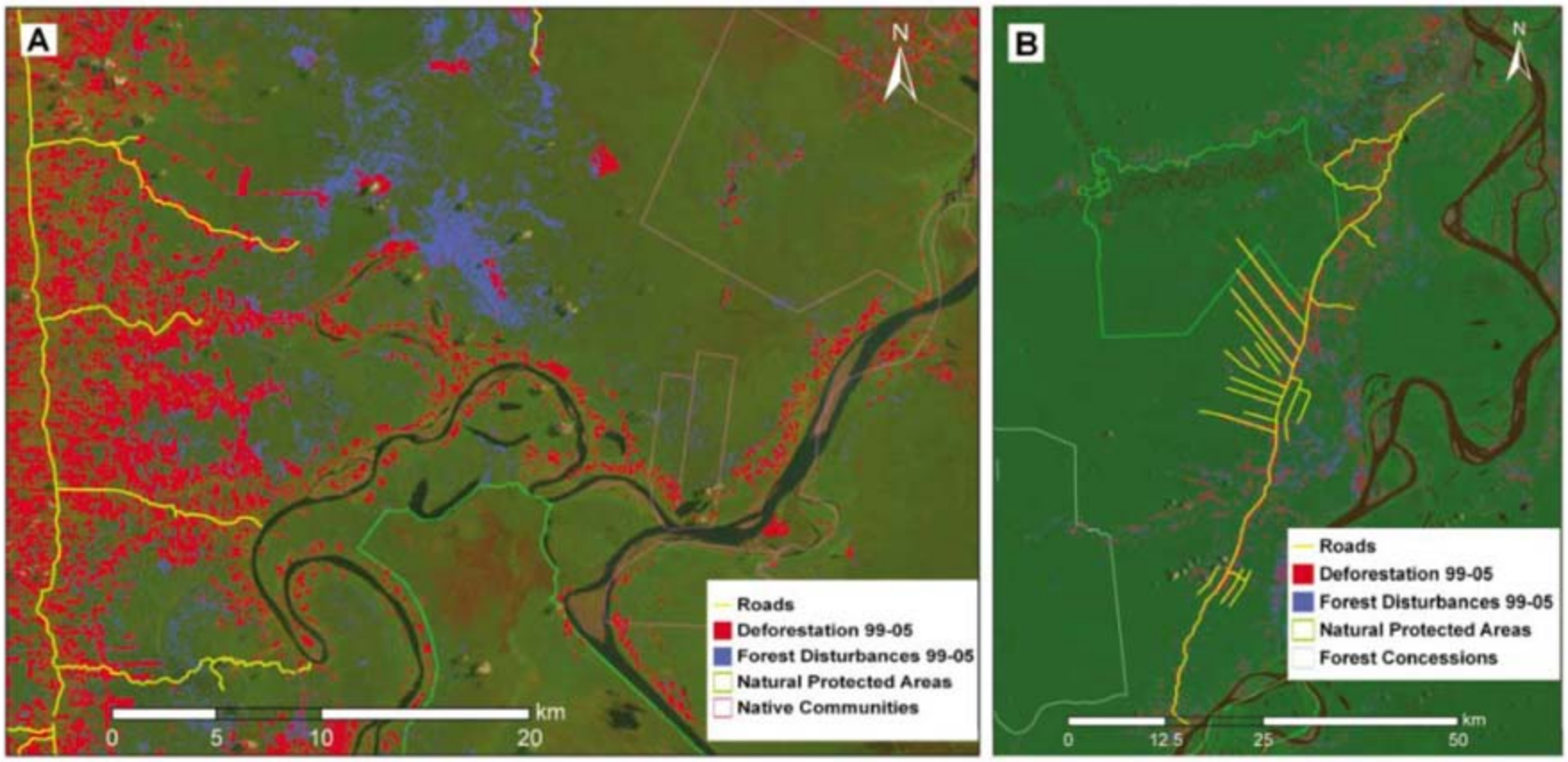

Fig. 2. Two high-resolution examples of forest disturbance and deforestation detection from CLAS overlaid on satellite imagery, showing impacted forest (**A**) near Pucallpa (left), where damage is more extensive in nonprotected areas accessible from roads or rivers, and (**B**) near the remote area of Iquitos (right) with small damage (see fig. S1 for location).

Table 2. Percentage of detected forest disturbances and deforestation that falls within the boundaries of natural protected areas and indigenous territories of the Peruvian Amazon. Geographic information system (GIS) spatial layers obtained from the Peru 2000 Forest Map, INRENA. Spatial layers of titled indigenous territories have their basis in unpublished data collected and prepared by the Instituto del Bien Común for an ongoing study, in which territories of 80% of titled indigenous groups had been mapped. Analysis also included Madre de Dios State Reserve (Indigenous Peoples in Voluntary Isolation) spatial layer from Centro de Información Forestal–INRENA, 2005.

	Damage within natural protected areas (%)		Damage within indigenous territories (%)	
Year	Disturbed	Deforested	Disturbed	Deforested
1999–2000	3	1	12	8
2000–2001	3	1	11	7
2001–2002	2	1	15	10
2002–2003	1	1	11	9
2003–2004	2	2	12	16
2004–2005	2	1	6	5
1999–2005	2	1	11	9

appear to be related to proximity to roads, indicating that the protection afforded by their legal status may not be sufficient when the land is highly accessible to markets (*6*). In fact, an estimated 75% of the total Peruvian Amazon forest damage, including 66% of disturbances and 83% of deforestation, was detected within a 20-km distance from the nearest roads (Fig. 1). However, even within that 20-km buffer, forests within conservation units were more than four times better protected against deforestation than unprotected forests (*21*). Even after compensating for differences in the geographic extent of each land-use type, forest damage was about 18 and 10 times more likely in undesignated and indigenous territories, respectively, than in natural protected areas (*21*).

We also evaluated the impacts of recent timber harvest legislation on rates of forest disturbance and deforestation, before and after their enactment (*11*). Within all permanent production forests allocated to long-term concessions between 2002 and 2004, deforestation rates were up to two orders of magnitude smaller than forest disturbance resulting from the logging operations (table S5). However, outside the concession areas granted in 2004 in the remote northern Iquitos region, disturbance and deforestation rates increased by 468% and 304%, respectively. This leakage effect was also prevalent in the central Pucallpa logging region, where deforestation and forest disturbances outside concessions rose almost 400% to a combined rate of 1086 km^2 in 2005. Furthermore, the Madre de Dios logging region observed an increase within and outside concessions but still at relatively low rates. These results suggest that sanctioned forest extraction activities may be an effective deterrent against forest clear-cutting, but closer monitoring of neighboring nonconcession lands is critical to prevent leakage around concession forests. A time-series analysis of our data shows that the rate of clear-cutting previously disturbed forest was 1.8%, 7.2%, and 13.8% at 1, 3, and 5 years, respectively, after the initial disturbance (table S10). These relatively low values suggest that forest disturbances in the Peruvian Amazon are not simply a precursor to deforestation.

Our field validation studies showed that the CLAS methodology is precise and accurate in detecting forest disturbance and deforestation in the Peruvian Amazon. Our uncertainty was 10.5% for forest disturbances and 0.5% for deforestation (table S6). Atmospheric correction, cloud cover, and annualization errors in the satellite analyses were found to be very low and had been proven nearly negligible compared with manual audit uncertainty (*15*, *21*).

The establishment of protected natural areas, the titling of native territories, and the sanctioning of selective logging activities have combined with the Peruvian Amazon's traditional conservation allies—its remoteness and a complex hydrological network—to ensure a moderate level of success in the conservation of its forest eco-

systems. Economic development of the forest sector, which employed 279,000 people nationally in 2001 (*24*), is essential for the well-being of human populations, but poorly monitored logging concessions, along with the challenges of uncontrolled road access, may hinder efforts to maintain ecological functions and diversity in Peruvian rainforests in the future. Deforestation pressures, along with rising rates of forest disturbance, in many tropical countries are often at odds with increasing conservation efforts (*25*, *26*). A balanced portfolio of forest use and protection, along with substantive law enforcement, could be used to sustain the services provided by tropical forests to society while also protecting those forests. Increased satellite monitoring of logging and other forest disturbances will thus be essential to conservation, management, and resource policy development efforts in Peru and other rainforest nations.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/1146173/DC1
Materials and Methods
Fig. S1
Tables S1 to S10
References

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POSTDOCTORAL OPPORTUNITIES

POSTDOCTORAL POSITION

A Postdoctoral position at the U.S. Environmental Protection Agency (EPA) administered through North Carolina State University (NCSU) as part of the EPA/NCSU cooperative agreement is available to investigate the toxicity of perfluoroalkyl acid (PFAA). PFAAs (such as perfluorooctanoic acid [PFOA], and perfluorooctane sulonfate [PFOS]) are environmentally persistent chemicals that have been detected in the general population. The human health risk assessment of these chemicals is currently being conducted by the Office of Prevention, Pesticides, and Toxic Substances (OPPTS) at EPA, as well as by various regulatory agencies around the world. Some toxicity profiles recently identified by EPA Laboratories include developmental toxicity, hepatotoxicity, and alterations of thyroid hormone homeostasis. Ongoing research is directed to gain a better understanding of the modes of action of these chemicals, in order to facilitate the extrapolation of data from animal models to human health risk assessment. The research project for this Postdoctoral position involves studies to determine the mode of action of PFAAs on thyroid hormone imbalance and on liver hypertrophy and lipid transport and metabolism, including possible participation of the PPAR pathway. A Ph.D. in biology, chemistry, or related field is required. Experience with small animals (rodents) studies and biochemical and physiological assays are essential. Knowledge of thyroid hormone metabolism and lipid biochemistry is preferred. *Candidates must be U.S. citizens or permanent residents.* Salary will commensurate with experience. Send letter of interest, resume, and names and addresses of three references to: **Dr. Kenneth B. Adler, College of Veterinary Medicine, North Carolina State University, Campus Box 8401, Raleigh, NC 27606.**

The University of Michigan Chemistry Fellows Program is seeking applications from outstanding individuals to become the first **MICHIGAN FELLOWS in CHEMISTRY.** This new postdoctoral Program, housed in the Department of Chemistry, is geared towards exceptional scientists who are just completing, or have recently completed, their Ph.D. studies. The program will combine a competitive salary ($50,000 annually for two years plus benefits), exciting research programs, and professional development opportunities specifically designed for each candidate.

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Full details of the nomination and application process and the opportunities available in the Michigan Chemistry Fellows Program can be found at **website: http://www.umich.edu/~michchem/fellows/.** Questions about the program can be directed to **e-mail: chemfellows@umich.edu.** *Women and minorities are encouraged to apply. The University of Michigan is supportive of the needs of dual-career couples and is a nondiscriminatory, Affirmative Action Employer.*

POSTDOCTORAL POSITION at the University of Wisconsin, Madison, available immediately to investigate the electrophysiological properties of human embryonic stem cell-derived cardiomyocytes as models of human cardiac physiology and disease. Experience in patch clamp technique and cardiac biology required. Salary will be commensurate with experience. Please send curriculum vitae, three references, and statement of research interests to: **Timothy J. Kamp, M.D., Ph.D., Box 3248 CSC, 600 Highland Avenue, Madison, WI 53792** or **e-mail: tjk@medicine.wisc.edu.**

POSTDOCTORAL OPPORTUNITIES

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David Geffen School of Medicine at UCLA

A position for a Postdoctoral Fellow is available to study excitation-contraction coupling in cardiomyocytes with genetically altered levels of the sodium-calcium exchanger. We have especially interesting data on the adaptations of mice in which the sodium-calcium exchanger has been knocked out (*Circ. Res.* **95**:604-11, 2004). The project involves application of electrophysiological and imaging techniques to isolated myocytes and provides an excellent training opportunity. Experiments are done in collaboration with **Dr. Josh Goldhaber.** We prefer applicants with electrocardiogram coupling or electrophysiological experience though this is not essential. Research will be carried out in the Cardiovascular Research Laboratories in the School of Medicine at UCLA. Applicants should send curriculum vitae including the names of three references to **Dr. Kenneth Philipson (e-mail: kphilipson@mednet.ucla.edu).**

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Position available immediately in the systems neuroscience Laboratory of **Douglas Nitz.** Under study are the neural mechanisms underlying decision making. Specifically, research is focused on the integration of cortical and subcortical (basal ganglia) inputs to the premotor region of the rat neocortex. To this end, multiple single unit recordings are obtained within premotor cortex and, simultaneously, from three brain regions bearing projections to premotor cortex. Work in behaving animals is paralleled, in adjoining laboratories, by molecular and in vitro experiments having the same research focus. The ideal candidate will have experience in obtaining single unit recordings from behaving animals and will be capable of designing and implementing novel behavioral paradigms as well as analyses of multiple unit recordings. Send curriculum vitae and contact information for three references to: **Douglas Nitz, Ph.D., The Neurosciences Institute, 10640 John Jay Hopkins Drive, San Diego, CA 92121. E-mail: nitz@nsi.edu.**

POSTDOCTORAL RESEARCHER, MOLECULAR ECOLOGY. University of Illinois at Chicago is seeking a researcher to develop primers to prey DNA as part of a project investigating food-web structure. Applicant must have completed Ph.D. and demonstrated broad expertise in molecular biology techniques. Position is for two years starting early 2008. E-mail curriculum vitae, PDFs of publications, and three letters of reference to **e-mail: dhwise@uic.edu.** Details at **website: http://www.uic.edu/labs/wiselab/.**

Training Postdocs: Communication Is Key

The most important factors for ensuring a successful postdoctoral experience are honest and open communication with mentors, according to postdoc supervisors who responded to a survey carried out for *Science* Careers. Here, they provide some strategies and tips for effective communication and for teaching graduates how to communicate better.

By Laura Bonetta

The postdoctoral years are typically a stepping-stone to an independent position as the head of an academic or industrial laboratory. To ensure they are on this career trajectory, postdocs rely on regular feedback from their supervisors, who may also give advice and training on various competencies, from writing papers and giving presentations, to seeking funding and landing a job.

It is no surprise then that communication, closely followed by mentoring, ranked as the most important factor contributing to a successful postdoc appointment in a recent survey of supervisors by *Science* Careers. "It is important to show your postdocs that you are there for open and honest discussion. And not that you are the kind of boss where they have to knock on the door and make an appointment. My door is always open," says **Keith Rose,** a professor at the University of Geneva and founder of the proteomics company GeneProt.

> "You can be the most brilliant genius at the bench but if you cannot communicate your results they have no impact."

Why Communicate?

Rose was one of the over 800 postdoc supervisors polled in this year's survey (see "Survey Methodology"). Ninety-four percent of them rated communication as important or very important in contributing to a successful postdoc experience. "Communication is the key that unlocks all the other doors," says **Alyson Reed,** executive director of the National Postdoctoral Association. "You can be the most brilliant genius at the bench but if you cannot communicate your results they have no impact."

But the value of communication may not be as immediately obvious to postdocs themselves. In a complementary survey conducted in 2004, which polled postdocs, communication came in ninth on a list that included mentoring, direction and vision, funding, networking, advancement opportunities, work culture, training, and employer situation. "When given a laundry list of things to rank, communication may not pop out, when compared to items like funding or training," says Reed.

Indeed, sometimes postdocs view weekly or monthly group meetings as an imposition on their time. "At our lab meetings I expect a formal presentation. It takes a lot of time and sometimes postdocs don't like it," says **Naglaa Shoukry,** an immunologist at the University of Montreal, Canada. "When I was training I found presentations frustrating. But now when I look back I see it was important."

Rose agrees. Although most people in his lab are French-speaking, the meetings are carried out in English. "When my Corsican postdoc had to go to a conference on my behalf to give a presentation, he would not have done as well if he had not practiced every week," says Rose. "It is very important to learn to present clearly."

What to Communicate?

In addition to weekly group meetings, many supervisors schedule regular one-on-one get-togethers with their postdocs to discuss their experiments and lab issues. During the three years of running her own lab, Shoukry has learned that it is better to deal with problems right away, rather than letting things brew. "Sometimes I can feel that something is wrong in the lab, and I will directly ask my postdocs," she says. She also encourages her postdocs to tell her about any difficulties in obtaining data. "I let them know I don't expect that everything will go smoothly," she explains.

Clearly laying out expectations, providing regular feedback, and ensuring good interaction and discussion within the group are the key communication traits that describe a good supervisor, according to survey participants (96 percent to 97 percent agreed or strongly agreed that continued »

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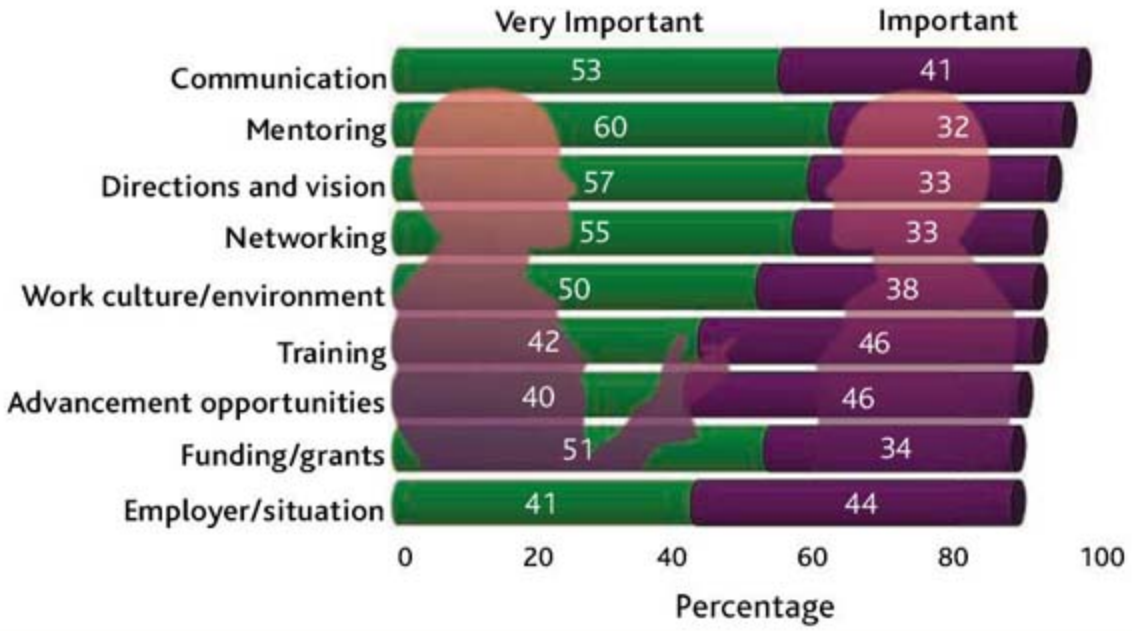

these were important). Shoukry makes sure her postdocs are aware of her expectations even before they join the lab. She goes through a mental checklist at the first meeting with a prospective postdoc to explain that she wants them to work hard, keep a lab notebook, be available during regular work hours, and so on. "You have to be frank right from the start. And you have to put it bluntly, so that there are no misunderstandings," she says.

The Power of Evaluations

Some postdoc supervisors also rely on formal evaluations for giving feedback. "Each employee at the Lawrence Berkeley National Laboratory (LBNL) goes through an annual process of evaluation," says physicist **Natalie Roe.** "It forces everyone, at least once a year, to check in."

The evaluations consist of a set of questions regarding goals and achievements to be completed by the postdocs before meeting with their supervisor, who then writes up the final document. "I usually take what they accomplished word for word but may add some details," says Roe. "Often people underplay what they have accomplished. They will think something they have done is routine, but instead it may be something that will be looked on favorably when they are looking for a job."

When she meets with her postdocs to discuss the responses, Roe takes the opportunity to review their career trajectory. "At LBNL a postdoc is generally considered to be a three-year position," she explains. "So you need to be on the road to getting a job at the appropriate time."

Industry Versus Academia

Being "on track" is critical for those training in industry, according to **Matthew Silver,** a postdoc at Wyeth Research in Cambridge, Massachusetts. Silver chose an industrial postdoc position because he ultimately wants to pursue a career in industry. "The main focus for my position is research, but I also get exposed to industrial culture," he says. But unlike postdoctoral positions in academia, his is only a two-year appointment (albeit with the possibility of two six-month extensions). "You don't want to go down the wrong path for too long," he says. "It is critical to talk about your career with your supervisor when you are only doing a postdoc for a short period of time."

Robert Martinez was hired at a staff scientist at Wyeth in 2001 after completing a four-year postdoc at the Dana-Farber Cancer Institute in Boston. He agrees that postdocs in industry cannot afford to flounder—and not only for the sake of their own careers. "Obtaining a postdoctoral fellow to work in your lab is a competitive process at Wyeth. A supervisor has to apply for the position. So it is important that his or her postdoc be successful," says Martinez. "It is important to maintain a very solid record."

To motivate his postdocs to be productive, Martinez holds monthly seminars where lab members give 20-minute presentations of their research. "I make sure I always attend those meetings," says Martinez. "And I tell them, 'If you have talked about something before, I don't want to hear it again.'"

How to Motivate

Most supervisors, like Martinez, would like their postdocs to work hard and be passionate about their projects. Although you cannot force someone to care about what they are doing, there are ways—such as giving postdocs as much choice as possible over what projects to pursue and ownership over the work—to encourage productivity. "Sometimes postdocs lose motivation if they feel that the project is not theirs," says **Ana Gamero,** principal investigator at the National Cancer Institute in Frederick, Maryland. "After a postdoc has spent three years in a lab, there are usually so many projects in place that the supervisor cannot continue with every project. I let them know I am always willing to give something up."

Another motivator is rewarding achievements. "To excite them about the work they are doing I may encourage a postdoc to submit an abstract and attend a conference or to talk to a guest speaker and go out for dinner," says Gamero. "I want them to see something beyond being a postdoc."

Attending conferences and meeting other scientists provide a chance for postdocs to establish useful connections. Postdoc supervisors who participated in this year's survey ranked networking as the fourth most important factor (tied with training) contributing to a successful postdoc experience. But, whereas 51 percent of supervisors strongly agreed that providing opportu- continued »

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STEM CELL BIOLOGY GROUP

Reference number: PI/07/05

A position is available to study the epigenetic regulation of early haematopoietic development using embryonic stem (ES) cell differentiation. The major aim of the lab is to better define the molecular and cellular regulation of commitment to the haematopoietic lineage during early development. You should have expertise in molecular and cellular biology. Experience in the field of embryonic stem cells and/or haematopoiesis would be desirable.

Informal enquiries to Dr George Lacaud: glacaud@picr.man.ac.uk

STROMAL-TUMOUR INTERACTION GROUP

Reference numbers: PI/07/06 and PI/07/07

Two positions are available to study tumour microenvironment. The major aim of the laboratory is to elucidate molecular mechanisms by which tumour microenvironment promotes carcinoma cell invasion and metastasis, focusing on myofibroblasts frequently present within the stroma of human invasive breast carcinomas. (Orimo A. et al, Cell, 121, 335-348, 2005; Orimo A. and Weinberg R.A., Cell Cycle, 5, 1597-1601, 2006).

Informal enquiries to Dr Akira Orimo: aorimo@picr.man.ac.uk

CELL DIVISION GROUP

Reference number: PI/07/09

A position is available to study how fission yeast cells control entry to mitosis and how these controls are altered to accommodate changes in the environment. The project will employ a diverse range of techniques to study the spindle pole component Cut12 that acts with polo kinase to control commitment to mitosis (Genes & Dev 12: 914; Genes & Dev 17: 1507 Nature 435: 507). Mass spectrometric analysis of phosphorylation sites will be followed by genetic, biochemical and imaging approaches to address the functional significance of these sites. You should have a background in biochemistry and/or cell biology.

Informal enquiries to Professor Iain Hagan: ihagan@picr.man.ac.uk

INOSITIDE LABORATORY

Reference number: PI/07/12

A position is available to study the role of phosphoinositides in the development of cancer related phenotypes. The aim of the lab is to understand how phosphoinositides are modulated and used as second messengers in different subcellular compartments. You should have expertise in molecular and cellular biology. Experience in studying phosphoinositides is not essential.

Informal enquiries to Dr Nullin Divecha: ndivecha@picr.man.ac.uk

CELL SIGNALLING GROUP

Reference number: PI/07/08

A position is available to study post-translational modifications of Rac GTPase Exchange Factors (GEFs) required for distinct aspects of the neoplastic, transformed phenotype. Characterisation would also entail identifying interacting partners under these conditions. Ideally, you should have expertise in molecular and cellular biology, as well as biochemistry.

Informal enquiries to Dr Angeliki Malliri: amalliri@picr.man.ac.uk

LEUKAEMIA BIOLOGY GROUP

Reference numbers: PI/07/10 and PI/07/11

Two positions are available to study the biology of leukaemia stem cells. The primary aim of the laboratory is to further understand the mechanisms that regulate maintenance of the self-renewing sub-fraction of cells within a malignancy, so-called cancer stem cells. Applications from candidates with broad experience in molecular biology are encouraged, although prior experience in any of the following techniques would be an advantage: xenogeneic and syngeneic transplantation model systems; generation and analysis of transgenic or knockout model systems; retroviral or lentiviral shRNA genetic knockdown techniques; culture of human primary normal or malignant haematopoietic cells.

Informal enquiries to Dr Tim Somervaille: tsomervaille@picr.man.ac.uk

CELL CYCLE GROUP

Reference number: PI/07/13

Three positions are available for highly motivated postdoctoral fellows to study the mechanisms by which eukaryotic cells preserve genome stability during chromosome replication. We aim to understand the roles and regulation of "Replisome Progression Complexes" that are built around the MCM helicase at DNA replication forks (Gambus A. et al, (2006), Nature Cell Biology, 8, 358-366; Labib and Gambus, Trends in Cell Biology (2007), 17, 271-278). A strong background in biochemistry and molecular biology would be an advantage.

Informal enquiries to Dr Karim Labib: klabib@picr.man.ac.uk

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Postdoc Survey

"Thirty percent of my day is devoted to things other than my own research."
—Todd Castoe

nities to attend scientific meetings describes a good supervisor, only 38 percent felt that way about providing opportunities to meet other influential researchers.

Why Mentor Well

According to the survey, most supervisors (61 percent) spend 20 percent or less of their professional time supervising their postdocs; the remainder (39 percent) spend more than 20 percent of their time doing so. A large majority (78%) feel that they have this balance just right, while 14% would prefer to spend more time supervising, and only 6% believe this responsibility to be taking too much of their attention. "My philosophy is I could focus on publishing 20 really good papers or also make sure that I train 20 really good scientists who then each publish 20 really good papers," says professor **Graeme Mardon** at Baylor College of Medicine. "In the end mentoring makes a greater contribution. For me it is more satisfying to see someone develop than the nuts and bolts of running a lab."

So in which areas do postdocs most need mentoring? The top three general responsibilities for supervising postdocs identified by survey participants were discussing research project and direction (96 percent), reviewing data analysis and interpretation of results (91 percent), and assisting with writing manuscripts and seminar preparation (84 percent). Fewer supervisors cited providing guidance for career planning (75 percent) and helping to write grants and assist with funding efforts (64 percent).

"I never write my postdocs' papers," says Mardon. In his lab, postdocs write the first draft and then go through several revisions before the paper is submitted. "One of the arguments against doing it this way is that if you work in a very competitive field, you have to get papers out quickly," says Mardon. "But I have never gotten scooped because of the writing. If we got scooped, it was because we took longer to finish the work than another group."

Another important skill for postdocs to master is how to write grants. "I let the best grad students and postdocs in my lab see the entire R01 grant and write portions of it," says Mardon. Although Mardon's first R01 was funded, even though he had never before seen a grant application, he says the funding situation has become much more challenging. "It is also absolutely valuable to sit in study sections and see grants being torn apart. You learn what works and what does not work," he laughs. "I try to pass all this information along to my postdocs."

Managing the Work of Others

The majority of survey participants agreed that conducting high quality research (79 percent), learning to work independently (66 percent), and publishing work (66 percent) contributed to a successful postdoc experience. Learning to manage and supervise others ranked relatively low on the list (15 percent). Yet, most postdoc supervisors say that managing people is one of the toughest skills for scientists to learn.

Kyle Dawson, a postdoctoral fellow at the LBNL, has been given the chance to supervise undergraduate students in his lab, choosing projects for them and writing their evaluations. Being involved in a large collaborative project with several labs, he also had to recruit graduate students to join the project. "I did not know how to do that so I got advice from one of my advisers," said Dawson, who has two advisers from two different labs, including Roe, the physicist.

Dawson has also been involved in writing proposals, organizing communications among collaborators from 10 different universities, networking with other scientists, and coordinating their activities. "It has been a real learning experience," he says. "I had to put myself in the fire and just do it."

Well-Rounded Training

Like Dawson, **Todd Castoe,** a postdoc at the University of Colorado Medical School, received training in a variety of skills, beyond conducting experiments. "My adviser is giving me a lot of firsthand experience with the practicalities of running a lab. We talk about why we should finish specific projects and how that relates to current and future grants. We look at a pile of new data and decide what direction is most profitable to follow up," he says. "I get to see the larger picture."

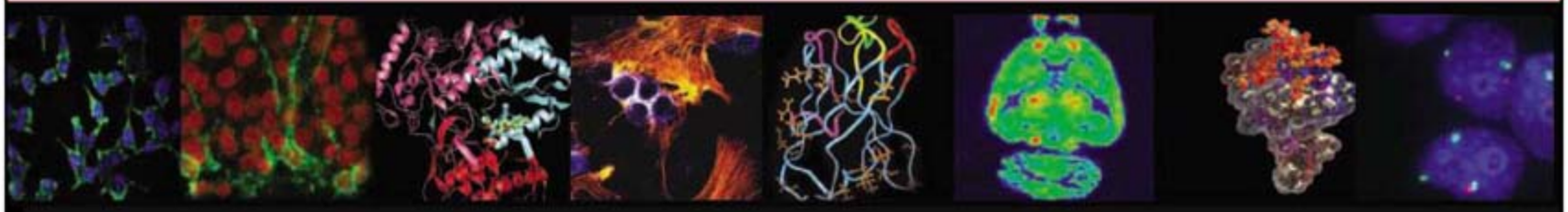
Castoe has been involved in writing grants, reviewing papers and then discussing them with his adviser, establishing collaborations, and working on grants for large projects. "Thirty percent of my day is devoted to things other than my own research," he says. Although he sometimes worries that all the added exposure will not be reflected on his CV when he starts to look for a job, he realizes that the training is preparing him to run his own lab. "I would call this one of the best-case scenarios for training. It is very holistic."

Communication has always been key to the scientific process. But as science becomes increasingly competitive and dependent on interdisciplinary, collaborative projects, communication skills—from interacting with others to presenting data at seminars to writing papers and grants to networking—will be even more critical to a scientist's success. Whether postdocs realize it or not, frequent and open communication with their supervisors and learning how to effectively communicate with their colleagues, will help ensure a successful transition from postdoc to independent researcher.

Laura Bonetta is a scientist turned freelance writer based in the Washington, D.C., area.

SURVEY METHODOLOGY

This year's survey aimed to determine what factors contribute to a successful postdoctoral experience from the supervisors' point of view. Starting in March 2007, 801 postdoc supervisors in the United States, Europe, and Asia responded online to a series of questions asking them to select the most important attributes for a successful postdoc experience and to rate the importance of various factors contributing to it. All survey participants were either currently supervising postdocs (78 percent) or had supervised postdocs in the past (22 percent). Half had six years or more of supervisory experience. The majority of survey participants were located in the United States and Canada (76 percent), while another 9 percent were in Europe and the United Kingdom, and 10 percent in Asia and the Pacific Rim.



Wyeth Research Postdoctoral Program

At Wyeth, we are recruiting outstanding, recent Ph.D. recipients who are interested in pursuing high-impact basic research, while observing first-hand the excitement and challenges of drug discovery. Postdoctoral positions are available in the following areas:

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INFLAMMATION
NEUROSCIENCE
CARDIOVASCULAR & METABOLIC DISEASES
ONCOLOGY
WOMEN'S HEALTH AND MUSCULOSKELETAL BIOLOGY

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www.wyeth.com/careers

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Toxicology Postdoctoral Traineeships

Postdoctoral Traineeships are available in various areas of Toxicology. The research studies are conducted with senior scientists at the Environmental Protection Agency at Research Triangle Park or Chapel Hill, North Carolina. The administrative appointments of the trainees are at the Curriculum in Toxicology, University of North Carolina, Chapel Hill, NC.

AWARDS ARE LIMITED TO UNITED STATE CITIZENS OR PERMANENT RESIDENTS BECAUSE OF THE FUNDING SOURCE.

A candidate who is interested in a specific project is encouraged to contact the Research Advisor identified with that project. An application consists of an emailed applicant's curriculum vitae and the names and addresses of three references sent to BOTH the Research Advisor and to the Program Director at **david_holbrook@unc.edu**.

Project 1: Comparative Toxicity of Environmental Asbestos: Mechanistic and Susceptibility Studies in Rodents.

Project Description: This project focuses on understanding the relationships between physical properties of environmental asbestos from Libby, Montana, and other areas, mechanisms of toxicity, and genetic susceptibility of exposed individuals. Healthy adult rats, neonatal rats, and rat and mouse models of fibrosis and cardiovascular disease can be used to determine the relationships between fiber burden, exposure effects, mechanisms, and susceptibility. These studies will assist in understanding the health risks associated with living in Libby and communities affected by naturally occurring asbestos.

Research Advisor: Dr. Stephen Gavett, Pulmonary Toxicology Branch, Experimental Toxicology Division, U.S. EPA, MC B143-01, Research Triangle Park, NC 27711; phone: **919-541-2555**; email: **gavett.stephen@epa.gov**.

Project 2: Comparative Toxicity of Environmental Asbestos: In Vitro Assessment of Mechanisms of Injury and Mode of Action.

Description: This project focuses on in vitro methods to compare the ability of asbestos obtained from Libby, Montana, and other sources of mineral fibers to cause significant biological effects in cultured cells. Research is needed to understand the effects of the mineral fibers on cell toxicity, cell function, signaling pathways, and gene expression in a variety of cell types. The effects studied will be compatible with those in animal toxicology studies and will assist in understanding the health risks associated with living in Libby and communities affected by naturally occurring asbestos.

Research Advisor: Dr. Robert Devlin, Clinical Research Branch, Human Studies Division, U.S. EPA, MD 58D, Chapel Hill, NC; phone: **919-966-6255**; email: **devlin.robert@epa.gov**.

Project 3: Mechanistic investigation of perfluoroalkyl acid (PFAA) toxicity.

Description: PFAAs (such as perfluorooctanoic acid, PFOA, and perfluorooctane sulonfate, PFOS) are environmentally persistent chemicals that have been detected in the general population. There are two specific aims for this research project: (a) Thyroid hormones (T4 and T3) are reduced by exposure to PFOS and PFOA, but this profile of hormonal imbalance does not resemble that of the classical hypothyroidism, in that a corresponding elevation of TSH via the hypothalamic-pituitary feedback mechanism is absent. Results from our preliminary studies indicate that PFAAs may act by displacing the thyroid hormones from their binding proteins. However, the long-term physiological sequelae of this hormonal alteration require further elucidation. (b) PFOA and PFOS induce liver hypertrophy, in part through activation of the PPAR molecular signals. Genomics studies have indicated profound changes in the expression of genes responsible for lipid metabolism and transport, but the corresponding changes in lipid biochemistry and intermediary metabolism require further elaboration. Results from studies in our laboratories have indicated that in utero exposure to PFOA in the mouse leads to latent obesity in adulthood, and it is likely that the chemical influences the manners with which the adipocytes handle lipid transport and metabolism. An understanding of the mechanisms of PFOA action (whether through the PPAR pathway or others) will better characterize the health risk potentials of this chemical.

Research Advisor: Dr. Christopher Lau, Reproductive Toxicology Division, MD-67, US EPA, Research Triangle Park, NC 27711; Telephone: **(919) 541-5097**; email: **lau.christopher@epa.gov**.

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Postdoctoral Positions

The University of Alabama at Birmingham (UAB) is one of the premier research universities in the US with internationally recognized programs in AIDS and bacterial pathogenesis, bone biology and disease, cancer, diabetes and digestive and kidney diseases, free radical biology, immunology, lung disease, neuroscience, trauma and inflammation, and basic and clinical vision science among others. UAB is committed to the development of outstanding postdoctoral scientists and has been consistently ranked in recent years as one of the top 10 locations among US universities for training postdoctoral scholars.

UAB is recruiting candidates for postdoctoral positions in a variety of research areas. UAB faculty are well funded (20th in 2005 NIH funding), utilize multidisciplinary approaches, and provide excellent research training environments that can lead exceptional candidates to entry level positions in academia, government or the private sector. Full medical coverage (single or family), competitive salaries/stipends, sick leave, vacation, and maternity/paternity leave are offered with every position. Depending on the source of funding, other benefits may be available. Birmingham is a mid-size city centrally located in the southeast near beaches and mountains and enjoys a moderate climate for year round outdoor activities and a cost of living rate lower than most metropolitan areas.

Visit our web site at **www.postdocs.uab.edu**, under Postdoctoral Opportunities to view posted positions. Send your CV and cover letter to the contact name for those positions for which you are qualified and which interest you. **University of Alabama at Birmingham, Office of Postdoctoral Education, 205-975-7020**.

UAB is an Equal Employment Opportunity Employer.

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

Research Associateship Program

Postdoctoral Research Awards
Senior Research Awards
Summer Faculty Fellowships
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offered for research at
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Opportunities for postdoctoral and senior research in all areas of science and engineering

- Awards for independent research at approximately 100 participating laboratory locations
- 12-month awards renewable for up to 3 years
- Annual stipend $41,000 to $70,000 - higher for senior researchers
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Detailed program information, including instructions on how to apply, is available on the NRC Web site at :

www.national-academies.org/rap

Questions should be directed to :

National Research Council
TEL: (202) 334-2760
E-MAIL: rap@nas.edu

Qualified applicants will be reviewed without regard to race, religion, color, age, sex or national origin.

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

CURIOUS MINDS

At Schering-Plough Biopharma, you'll put your curiosity to work in a scientific environment committed to breakthrough innovation in research and discovery. Combining the strengths of DNAX and Canji, Schering-Plough Biopharma has elevated its mission to new heights. When you conduct science in our biotech environment, with all the power, reach and resources of a large pharmaceutical company, you'll face new challenges and grow as an individual and as part of a team.

Postdoctoral fellowships are available in the following laboratories:

Robert Pierce, MD – We will examine the regulation and expression of specific myeloid-restricted receptors in tissue macrophages. Although not restricted to the liver, our initial focus will be on understanding the role of these receptors in affecting Kupffer cell function, in order to identify a means of therapeutic modulation of Kupffer cell activity. Specifically, the role of myeloid receptor signaling in relevant mouse models of hepatitis will be studied. Req #20060BR

Daniel Cua, PhD – The goal of this project is to a) study inflammatory mediators in committed T-cell lineages, b) study autoimmune-mediated inflammatory diseases, and c) examine the role of inflammatory cytokines in cardiovascular disease and the role of these cytokines in myeloid clearance of lipid laden plaques. Req #20061BR

Daniel Gorman and Rob Kastelein, PhD – Elucidate the biology of several novel C1q/TNF family members, using transgenic and KO mice; determine the cellular source of these proteins, determine their target cells, identify their receptors and signaling pathways, and test their role in disease, utilizing mouse models to determine their potential therapeutic utility. Req #20062BR

Kathy Miller, PhD – The project will involve engineering bispecific antibodies for applications in cancer therapy. Working closely with Biologists to select the most appropriate targets and applications, various bispecific antibody formats will be investigated that can either block or redirect cellular biology to kill tumor cells. Req #20063BR.

David Parry, PhD – Components of the nucleotide and DNA biosynthetic pathways represent attractive targets for oncology drug discovery. Many of the rate-limiting enzymes involved in these processes interact functionally and genetically with a number of cellular checkpoint mechanisms. We are looking for a postdoctoral fellow to develop genetic screens and validate functional assays of mechanism-based target inhibition, with a focus on cellular checkpoint activation. Experience in **conditional** lethal screen design and/or utilization of siRNA technology would be an advantage. Req #17884BR

To apply, please visit the Schering-Plough career website at:
www.schering-plough.com/schering_plough/careers/careers.jsp
and enter the Req # referenced above when searching.

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University of North Dakota
School of Medicine and Health Sciences
COBRE grant
Post-Doctoral Fellows

The University of North Dakota (UND) School of Medicine and Health Sciences recently renewed its $10.1 M 5-yr COBRE grant (**www.med.und.nodak.edu/cobre**) from the NIH for the continued development of a Center of Excellence in the "Pathophysiology of Neurodegenerative Diseases". UND is committed to the continued expansion of this neuroscience initiative focused on exploring mechanisms of neurodegenerative diseases and the development of therapeutic intervention strategies. The UND School of Medicine maintains state-of-the-art core facilities in mass spectrometry, confocal microscopy, electron microscopy, micro-PET, and a 16,000 square foot Neuroscience Research Facility which houses 7 COBRE investigators. The following project leaders are looking for motivated post-doctoral fellows.

Dr. Brij B. Singh works on calcium, TRPC channel and neuronal function using whole animals, electrophysiology, molecular, biochemical, and imaging techniques.

Dr. John A. Watt works on mechanisms by which neurotrophins and ketogenic factors promote neuronal survival and process outgrowth in the damaged CNS using stereotaxic surgery, organotypic slice cultures, immunocytochemical, molecular, ultrastructural and biochemical techniques.

Dr. Othman Ghribi works on links between environmental factors and the pathogenesis of Alzheimer's disease using animal and slice culture models as well as cell biology, molecular biology and advanced imaging techniques.

Dr. Thad A. Rosenberger works on lipid-mediated signaling in brain injury using a variety of modern techniques including animal surgery, tissue culture, chromatography, mass spectral analysis, RT-PCR, enzyme assay, gel electrophoresis, and Western blot analysis.

Dr. Saobo Lei works on neurotransmitter and neuropeptide receptor regulation of synaptic function and pathogenesis of neurological disorders such as epilepsy and anxiety using electrophysiological, molecular biology, and immunocytochemical approaches.

The University of North Dakota, with over 12,000 students, is located in family-friendly Grand Forks, North Dakota, a community of over 50,000 people with excellent schools, parks, and abundant year-round outdoor recreational activities. These positions offer competitive salaries and benefits packages. Interested individuals should send curriculum vitae, along with contact information and references to:

Jonathan D. Geiger, Ph.D.
Chair, Department of Pharmacology, Physiology, and Therapeutics
University of North Dakota,
School of Medicine and Health Sciences
501 North Columbia Road, Mail Code 9037, Rm. 3700
Grand Forks, North Dakota 58202

Office: **(701) 777-6221;** Fax: **(701) 777-4490**
Email: **jgeiger@medicine.nodak.edu**

The University of North Dakota is an Equal Opportunity Employer. Hiring is contingent upon eligibility to work in the United States of America.

POSTDOCTORAL FELLOWSHIP

Department of Dermatology, OHSU, Portland, Oregon
Training Program in Molecular Basis of Skin Pathobiology

Position for recent PhD, MD/PhD or MD (US citizen or Permanent Resident) in NIH-funded program for training highly qualified candidates for academic careers in basic & translational research in skin diseases, including cancer & psoriasis. OHSU Dermatology has a strong history of clinical & scientific research & a 40-year record in training dermatology residents including physician scientists & postdoctoral scientists on the path to independence. Program features a core of Dermatology faculty & a multidisciplinary network of scientists with int'l recognition in areas relevant to epithelial cell fate, development & diseases. The training program includes seminars in mentors' departments, Dermatology Research Division meetings & symposia, research forums tailored to postdoctoral students, & national/international meetings in cutaneous biology. Successful candidates desiring an academic career in basic or translational research in cancer or investigative dermatology using surface epithelial models can expect to receive training toward independence in research with a strong clinical translational component. OHSU is an equal opportunity employer; we encourage applicants from diverse backgrounds that may be underrepresented in academics & science. Applicants must be US Citizens/Permanent Residents.
For more information & application instructions see:
http://www.ohsu.edu/dermatology/research/training.php

OHSU OREGON HEALTH&SCIENCE UNIVERSITY

UNIVERSITY OF PENNSYLVANIA

NIH Sponsored Postdoctoral Training in Cell/Molecular Basis of Urological Diseases: Division of Urology invites applications from prospective postdoctoral fellows (Ph.D., D.V.M.-Ph.D., M.D.-Ph.D., or D.V.M. with residency training in pathology) with background in physiology, cell/molecular biology, or biochemistry. This training program differs from the conventional postdoctoral training in exposing the postdoctoral fellows to clinical problems, while carrying out cell/molecular biology research. The fellows will have exposure and opportunities to translate basic science information into new diagnostic, preventive and therapeutic strategies. The rapid and effective translation of basic scientific discoveries is greatly facilitated by mentoring from basic and clinical scientists.

The current research interests in the Division of Urology at the University of Pennsylvania Medical Center include (1) alterations of intracellular kinases, phosphatases, and anchoring proteins in smooth muscle urological diseases, (2) smooth muscle signaling mechanisms and regulation in diabetes and smooth muscle remodeling, (3) study of the cell/molecular basis of urinary incontinence, and voiding dysfunction, (4) connective tissue matrix remodeling, and (5) prostate and bladder cancer. However, the program is flexible and any other topics related to urogenital system may be accommodated by recruiting mentors with appropriate expertise from Penn's biomedical science community. Trainees will receive stipend at NIH level, health insurance and tuition for courses in molecular biology, gene therapy and urology.

Successful applicants should be highly motivated and have a (1) recent doctoral degree (obtained within last three years) in biomedical sciences from a U.S. or foreign University and (2) U.S. citizenship or immigrant status. Interested candidates should forward their CV and the names of two references to: **Dr. Samuel K. Chacko, Director of Basic Urological Research, University of Pennsylvania, 500 South Ridgeway Avenue, Glenolden, PA 19036-2307. Fax: 267-350-9610; E-mail: chackosk@mail.med.upenn.edu**. Start date September - October, 2007.

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LEADING MEDICINE™

Weill Cornell Medical College

The Department of Radiology, The Methodist Hospital and The Methodist Hospital Research Institute (TMHRI), Weill Cornell Medical College, Houston, Texas, USA

The Department of Radiology of The Methodist Hospital and the TMHRI are embarking on an ambitious program of molecular image guided diagnosis and therapy (MIGDT), merging the fields of molecular imaging, molecular biology, medical physics, and bioinformatics to transform interventional medicine. Several laboratories within our Department have immediate openings in postdocs positions.

- *Laboratories of Molecular Biology and of Systems Biology* investigate and apply molecular biology, cell biology, molecular pathology, and high throughput biotechniques to identify disease biomarkers in cancer, cardiovascular disease, neurodegeneration, and diabetes. The small animal imaging section uses both molecular biology and imaging technologies, which includes optical imaging, PET, SPECT, CT and MRI. Techniques such as RNA interference, adenoviral gene therapies and animal tumor models are also conducted.
- *Molecular Probes and Diagnosis Laboratory* develops novel molecular probes to sense molecular processes and disease–related targets, including tumorigenesis, cardiovascular disease, inflammation, stem cell biology, and gene therapy.
- *Conjugate and Medicinal Chemistry Laboratory* develops radiotracers and novel drug delivery and therapeutic techniques.
- *Laboratory of Medical Physics* designs and develops new multimodality and multi-scale imaging (CT, MRI, PET, optical, focused ultrasound, and in-vivo microscopy) technology and interfaces to medical robotics and devices for MIGDT.
- *Laboratory of Bioinformatics* investigates and develops new mathematical models, computational algorithms and software tools that enable MIGDT and extend genomics, proteomics, and systems biologic research.
- *Medical Image Computing Laboratory* focuses on the new algorithms and tools for in-vivo image analysis, multimodality fusion, and image data mining, in particular for neuroimaging and zebrafish imaging.

Postdoctoral positions in bio-organic/peptide/synthetic/medicinal/radio/fluorochrome chemistry, photodynamic therapy, molecular cloning, in-vivo optical microscopy, medical robotics, PET physics, computational genetics, systems biology, soft tissue image registration, oncology, and clinical neuroscience are immediately available.

Please e-mail CV and contact information with three referrals to **mehernandez@tmhs.org**; mailing address is: **Dr. Stephen Wong, Vice Chair and Chief of Medical Physics, Department of Radiology and Director, Bioinformatics Program, TMHRI c/o Martha Hernandez, the Methodist Hospital, 6565 Fannin Street - #B5-022, Houston, Texas 77030.**

STONY BROOK

POSTDOCTORAL POSITIONS

The Research Foundation of Stony Brook University/SUNY anticipates the following postdoctoral positions being available between Spring and Fall 2007.

• BIOCHEMISTRY AND CELL BIOLOGY

Role of O-Fucosylation of proteins containing Thrombospondin Type 1 repeats. Robert Haltiwanger, WC-R-4252-07-08-S

Glycoprotein synthesis and degradation. William J. Lennarz, WC-R-4255-07-08-S

Metabolic engineering of novel fatty acid accumulation in plant seeds. John Shanklin, WC-R-4256-07-08-S

Yeast chromatin modifying enzymes. Rolf Sternglanz, WC-R-4254-07-08-S

Regulation of Xenopus development by growth factor and ubiquitin pathways. Gerald Thomsen, WC-R- 4252-07-08-S

• CHEMISTRY

Ultra-/nano-filtration/reverse osmosis, water purification, multifunctional copolymers, polymer inorganic hybrids, polyoxometalates. Ben Chu, WC-R-4257-07-08-S

Polymer synthesis, nanocomposites, ultrafiltration/nanofiltration/reverse osmosis. Benjamin Hsiao, WC-R-4259-07-08-S

Computational structural biology and biophysics. Carlos Simmerling, WC-R-4258-07-08-S

• COMPUTER SCIENCE

Computer Science, Linguistics, or Economics: News and Blog Data Analysis Steven Skiena, WC-R-4260-07-08-S

• DEVELOPMENT INFARED SOURCES

Fabrication and characterization of the Infrared optoelectronic devices. Gregory Belenky, WC-R-4261-07-08-S

• ELECTRICAL AND COMPUTER ENGINEERING

Detectors in experiments on laser proton acceleration. Peter Shkolnikov, WC-R-4289-07-08-S

• GEOSCIENCES

Planetary Science: Chemical/Mineralogical evolution of Martian crust. Scott McLennan, WC-R-4263-07-08-S

Experimental Material/Mineral Chemistry. John Parise, WC-R-4262-07-08-S

• MOLECULAR GENETICS AND MICROBIOLOGY

Virus-host factor interactions involved in protein trafficking, assembly and particle release. Carol Carter, WC-R-4282-07-08-S

Regulation of Nuclear Signaling Pathways by the Adenovirus E4-ORF3 Protein. Patrick Hearing, WC-R-4264-07-08-S

• NEUROBIOLOGY AND BEHAVIOR

Synaptic mechanisms in the retina. Gary Matthews, WC-R-4266-07-08-S

Electrophysiology of the injured spinal cord. Lorne Mendell, WC-R-4265-07-08-S

Physiology of neuregulin signaling in CNS synapses circuits and behaviors. Lorna Role, WC-R-4267-07-08-S

• PHARMACOLOGY

Wnt Signaling in Mouse Development. Ken-Ichi Takemaru, HS-R-4270-07-08-S

Mechanisms of neuregulin signaling in CNS synapses circuits and behaviors. D. Talmage, HS-R-4269-07-08-S

• PHYSIOLOGY AND BIOPHYSICS

Biophysics of signal transduction: membranes, PIP2, calmodulin, EGFR. Stuart McLaughlin, HS-R-4268-07-08-S

To apply online and for information, visit *www.postdocs.stonybrook.edu*
or mail résumés to: Office of the President,
Stony Brook University, Stony Brook, NY 11794-0701.

Stony Brook University/SUNY is an affirmative action/equal opportunity educator and employer.

University of California
LAWRENCE LIVERMORE NATIONAL LABORATORY
Science in the National Interest

LAWRENCE POSTDOCTORAL FELLOWSHIP

The Lawrence Livermore National Laboratory (LLNL) has openings available under its Lawrence Fellowship Program. This is a highly desirable, prestigious postdoctoral position with ample resources and freedom to conduct cutting-edge research in a field of the candidate's choice. The duration of the Fellowship is up to three years. Typically two to four openings are available each year. Fellowships are awarded only to candidates with exceptional talent, credentials and a track record of research accomplishments.

Candidates will do original research in one or more aspects of science relevant to the mission and goals of LLNL which include: Physics, Applied Mathematics, Computer Science, Chemistry, Material Science, Engineering, Environmental Science, Atmospheric Science, Geology, Energy, Lasers and Biology. Successful candidates may participate in experimental or theoretical work at LLNL, and will have access to LLNL's extensive computing facilities, specialized laboratory facilities and field equipment. A senior scientist will serve as a mentor to each of the Fellows. The candidates will receive full management and administrative support. The salary is $8,092/mo.

Please refer to our web page **http://fellowship.llnl.gov** for eligibility requirements and instructions on how to apply. When applying and prompted, please mention where you saw this ad. The deadline for application is November 2, 2007. LLNL is operated by the University of California for the National Nuclear Security Administration/Department of Energy. We are an Equal Opportunity Employer with a commitment to workforce diversity.

Lawrence Livermore National Laboratory

http://fellowship.llnl.gov

Karolinska Institutet

POSTDOCTORAL FELLOWSHIP IN ORAL BIOLOGY

Full-time for one year, with a possibility to extend it with another year.

A postdoctoral position funded by a Swedish tax-free stipend is available with a group working on mineralized tissues. The main part of the project is focused on establishing osteogenic cell lines from human embryonic and mesenchymal stem cells. Use of gene therapy approach to express bone specific genes in the cells will enhance our knowledge of development, function and regeneration of bone tissue.

The applicant should have strong background in cell and molecular biology.

A scholarship for the pursuit of postdoc studies may be awarded for up to two years in the five years following the public defence (or equivalent) of a doctoral thesis.

The position is available immediately.

Applications should contain a C.V. with a summary of previous research experience and publication list and the names and contact details of two referees. Closing date 01 October 2007.

Application should be sent to:
Mikael Wendel, Ph.D, Karolinska Institutet,
Center for Oral Biology,
P.O. Box 4064, SE-141 04 Huddinge, Sweden
Mikael.Wendel@ki.se

JRC
EUROPEAN COMMISSION

itu Institute for Transuranium Elements

NMR investigations of actinide ions in solutions

Fellowship for senior scientist / post-doctoral researcher

The Institute for Transuranium Elements (ITU) in Karlsruhe, Germany, invites applications for a research fellowship in the field of Actinide Coordination Chemistry.

ITU is one of the seven Institutes of the Joint Research Centre, the service of the European Commission providing scientific and technical support for the conception, development, implementation, and monitoring of the European Union policies.

ITU is a reference centre for basic actinide research, with a broad range of analytical capabilities for the study of nuclear materials.

The final goal of this research is the development of extracting agents for the reprocessing of nuclear wastes. The successful candidate will oversee the design, installation and commissioning of a NMR spectrometer for the study of lanthanide and actinide ions in solutions. He/she will perform structural and dynamical studies of free and complexed ions, in order to understand the molecular details of the separation processes.

The appointment is for 2 years, with potential of an extension. The successful candidate must have a Ph.D. in chemistry and a strong background in NMR techniques and in coordination chemistry.

Informal enquiries may be made to the Director of the Institute, Prof. Dr. Thomas Fanghaenel **thomas.fanghaenel@ec.europa.eu**. For further details about ITU and the procedure for applying for the post please visit the ITU website at **http://itu.jrc.cec.eu.int/index.php?id=96** or write to: **jrc-recruitment-itu@ec.europa.eu**. Please quote reference C30/40-2007-09/01.

USDA ars Agricultural Research Service
www.ars.usda.gov

The USDA Agricultural Research Service (ARS), Corn Insects and Crop Genetics Research Unit in Ames, Iowa (Iowa State University campus) invite applications for a **RESEARCH GENETICIST/COMPUTATIONAL BIOLOGIST** (GS-11/12 $52,912-$82,446). The scientist will work with a team and collaborators to assemble analyze and annotate the full soybean genome sequence and make comparisons to genomes of related species. The project involves integration of genetic and physical map data, characterization of genomic sequence for features of interest, comparisons with other plant genomes, and preparation of public databases, online research tools, and journal publications. PHD in Genetics, Molecular Biology, Bioinformatics/computational biology or related field is required.

See complete job announcement and application instructions at:
http://www.afm.ars.usda.gov/divisions/hrd/hrdhomepage/vacancy/07074.htm

For additional information contact **Dr. Shoemaker** at telephone: **515-294-6233** or email: **Randy.Shoemaker@ARS.USDA.GOV**.

U.S. citizenship is required. The USDA is an Equal Opportunity Provider and Employer.

JRC
EUROPEAN COMMISSION

itu
Institute for Transuranium Elements

Opportunities for Research Fellowships at the Institute for Transuranium Elements

The Institute for Transuranium Elements (ITU) in Karlsruhe, Germany, is one of seven institutes of the Joint Research Centre, the service of the European Commission that functions as a reference centre of science and technology for the European Union. The mission of ITU is to provide the scientific foundation for the protection of the European citizen against risks associated with the handling and storage of highly radioactive elements. ITU's prime objectives are to serve as a reference centre for basic actinide research, to contribute to an effective safety and safeguards system for the nuclear fuel cycle, and to study technological and medical applications of radionuclides / actinides.

ITU offers research fellowships to young scientists and to established researchers who wish to participate in leading-edge research projects.

PhD-Students (category 20 research fellowship)

Cat. 20 fellowships are intended for PhD-students in the field of nuclear chemistry, physics or materials science.

Post-Doctoral Researchers (category 30 research fellowship)

Cat. 30 fellowships are intended for researchers in the field of nuclear chemistry, physics or materials science holding a doctoral degree or having fulfilled all the obligations to obtain a Ph.D. (certified by the University) at the time of the application.

Both programmes provide up to 3 years of support for fellows to train in world class research facilities, many of which are unavailable elsewhere in Europe. Fellows must be nationals of an EU Member State, an Associated State, an Associated Candidate Country or must have resided in a country of the European Union for at least five years prior to the start of the fellowship.

Senior Scientists and Experts (category 40 research fellowship)

This programme provides up to 2 years of access to a unique research infrastructure dedicated to nuclear science. Applications are welcome from any senior scientist with a proven reputation in the field of science relevant to the project proposals and who has, at the time of application, a minimum of 10 years research experience at post-doctoral level or a minimum of 16 years research experience at post-university level. Fellows must be nationals of an EU Member State, an Associated State, an Associated Candidate Country or must have resided in a country of the European Union for at least five years prior to the start of the fellowship. In exceptional cases, the senior researchers may be from another country.

The project proposals as well as guidelines for the application procedure are available on the ITU web site: http://itu.jrc.cec.eu.int/index.php?id=96. Closing date for applications is 30 September 2007.

Informal enquiries may be made to the Director of the Institute, Prof. Dr. Thomas Fanghaenel, **thomas.fanghaenel@ec.europa.eu**.
For further details about ITU please visit the ITU website **http://itu.jrc.cec.eu.int** or write to: **jrc-recruitment-itu@ec.europa.eu**.
Please quote "open call for research fellowships summer 2007".

POSTDOCTORAL OPPORTUNITIES

The Wadsworth Center of the New York State Department of Health, with basic and applied research programs in the biomedical and environmental sciences, provides a unique and dynamic postdoctoral training experience. Enhancing this environment are state-of-the-art core facilities; broad-based graduate programs with the University at Albany, State University of New York; and new initiatives in bioinformatics, genomics, nanobiotechnology, and biodefense. Positions are available in the following areas:

- **Atmospheric Chemistry**
- **Biodefense**
- **Biomarkers/Nutrition**
- **Cancer Biology/Chemotherapy**
- **Carcinogenesis**
- **Cell Biology/Mitosis**
- **DNA Repair/NMR**
- **Drug Metabolism/Resistance**
- **Gene Expression/Regulation**
- **Immunology**
- **Infectious Disease**
- **Medical Entomology**
- **Microbial Genetics/Pathogenesis**
- **Mobile Genetic Elements**
- **Neuroscience/Disease**
- **Stem Cell Biology**
- **Structural Biology**
- **Toxicology/Neurotoxicology**

For additional information, go to:
www.wadsworth.org/educate/postdocs.htm
and to apply, contact:
Dr. Donal Murphy, Research Office,
Wadsworth Center, New York State Department of Health
P.O. Box 509, Albany, NY 12201-0509
murphy@wadsworth.org

Wadsworth Center
New York State Department of Health
Health Research Incorporated

AA/EOE

Children's
National Medical Center

The **Glycobiology Program of the Center for Cancer and Immunology Research** at **Children's National Medical Center in Washington, DC** invites applications for a postdoctoral position (MD or PhD) in tumor biology with a focus on the tumor microenvironment and tumor progression. Experience in cellular and molecular biology and interest in development of genetic murine tumor models is sought. Applicants must have a demonstrated record of accomplishment, should possess excellent communication skills, and be U.S. citizens or permanent residents. Academic appointment is at the George Washington University.

Qualified candidates for this NIH funded position, available immediately, should send curriculum vitae and contact information of two references to: **Stephan Ladisch, MD, Director, Center for Cancer and Immunology Research, Children's Research Institute, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010; FAX (202) 884-3929; email sladisch@cnmc.org.**

POSTDOCTORAL OPPORTUNITIES

Senior PhD Scientist
In vivo Pharmacology – Infectious Diseases

The *in vivo* Pharmacology group within the Infectious Disease group is looking for a highly-motivated, innovative, and independent scientist to participate in a dynamic, fast-paced research setting focused on discovering and developing novel antibacterial therapeutics.

Responsibilities include developing and implementing *in vivo* infection models to support anti-infective drug discovery and early clinical development, providing innovative scientific leadership for *in vivo* pharmacology including pharmacokinetics and pharmacodynamics, and contributing to scientific discussions and formulate scientific initiatives. Other administrative duties include to supervise, lead, and develop a team of skilled scientific associates.

Requirements: The position requires a PhD degree in a relevant field with a minimum 5+ years of laboratory experience in industry or academic setting. Strong skills in *in vivo* Pharmacology, especially in the area of anti-bacterial drug research and development. The individual should have strong oral and written communication skills and a demonstrated ability to work in a team-oriented environment.

To view full job description and to apply, visit www.nibr.novartis.com and follow the links to Careers and Job Opportunities. Please be sure to reference **Job ID 28924BR** when you apply.

NOVARTIS

Novartis is an equal opportunity employer. M/F/D/V.

POSTDOCTORAL OPPORTUNITIES

Grant for Postdoctoral Positions in Sweden

The grant will enable researchers with Swedish or non-Swedish doctorates (PhDs or equivalent) to work at Swedish higher education institutions or research establishments. The programme will span two years. Research areas: Natural Sciences, Engineering Sciences, Medicine, Humanities, Social Sciences and Educational Sciences.
The last application date is September 25, 2007.

Further information is available at www.vr.se

Vetenskapsrådet

POSITIONS OPEN

Carnegie Mellon

Carnegie Mellon University is pleased to announce the creation of the

Ray and Stephanie Lane Center for Computational Biology

The Center will build on the strong history of computational and interdisciplinary research at Carnegie Mellon. It will seek to realize the potential of machine learning for expanding our understanding of complex biological systems by developing tools to enable automated creation of detailed, predictive models. We believe that these efforts will not only lead to deep biological knowledge but also to tools for individualized diagnosis and treatment of disease. One of the Center's key missions will be advancing the development of computational methods to improve cancer detection, diagnosis, and treatment. It will be directed by Robert F. Murphy, Ray and Stephanie Lane Professor of Computational Biology.

Faculty Openings in Computational Biology

We seek to recruit tenure-track faculty members who share the Center vision and appreciate the new challenges facing biology. These will include scientists who are interested in **developing new high throughput techniques** that will lead to better characterization of biological systems, using experimental and computational methods to **characterize and model biological systems at multiple scales**, and applying machine learning methods to biological systems.

We especially seek candidates who are interested in **integrating approaches to address complex questions related to improved cancer diagnosis and therapy** and developing and using combined **experimental and computational methods to study RNA structure, function and regulation**.

Appointments will be made in the Lane Center and in one or more academic departments, as appropriate to the background and interests of the candidate. New faculty members will be expected to both contribute to and benefit from the collaborative spirit that is a hallmark of Carnegie Mellon University and from the opportunities to collaborate with other institutions in the Pittsburgh region.

Lane Fellows in Computational Biology

The Center is pleased to solicit nominations for recent doctoral recipients to become Lane Fellows. The Program will recognize and support scientists of outstanding intellect who are dedicated to a career at the interface of computational and biological sciences so that they can pursue **postdoctoral** research in the rich computational environment at Carnegie Mellon. Candidates must be nominated by their thesis advisor, department head, or other faculty member from their Ph.D. granting institution who is familiar with their qualifications. Fellows will receive a stipend of **$54,000**, full fringe benefits, and a professional support budget for a period of three years. Nominations must be received by **October 1, 2007**.

For more information for potential faculty and fellow candidates, please see: **http://lane.compbio.cmu.edu**.

POSTDOCTORAL OPPORTUNITIES

POSTDOCTORAL FELLOWSHIP in molecular genetics at the Department of Health and Human Services (DHHS), National Institutes of Health (NIH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in Phoenix, Arizona. We are working to identify and characterize novel genes that cause Type 2 diabetes and obesity in humans. Applicants must have a Ph.D. or M.D. degree, with research experience in molecular biology. Please send curriculum vitae to: **Leslie Baier, Ph.D., NIDDK, National Institutes of Health, 445 North 5th Street, Phoenix, AZ 85004.** *This position is subject to a background investigation.* **E-mail: lbaier@phx.niddk.nih.gov.**

DHHS and NIH are Equal Opportunity Employers.

A **POSTDOCTORAL POSITION** is available studying fundamental mechanisms of eukaryotic transcriptional regulation. Projects involve in vitro reconstitution of transcription from TATA-less promoters, identification of new core promoter recognition factors, and studies of the mechanisms of transcriptional activation by nuclear respiratory factor 1 (NRF1) and its coactivators including PGC1 and the mediator complex. Individuals with a strong background in molecular biology and biochemistry are encouraged to apply. Extensive experience in eukaryotic transcription, chromatin, or related field is desirable. Applicants with limited experience but highly motivated with strong general background and good work ethic may be also considered. Send curriculum vitae, a description of research accomplishments and interests, and the names and telephone numbers, and e-mail addresses of three references to: **Dr. Shinako Takada, Department of Biochemistry and Molecular Biology at the University of Texas M.D. Anderson Cancer Center. E-mail: stakada@mdanderson.org. Website: http://www3.mdanderson.org/public/genedev/public_html/takada.html.**

M.D. Anderson Cancer Center is an Equal Opportunity Employer and does not discriminate on the basis of race, color, national origin, gender, sexual orientation, age, religion, disability, or veteran status except where such distinction is required by law. All positions at the University of Texas M.D. Anderson Cancer Center are security-sensitive and subject to examination of criminal history record information. Smokefree and drugfree environment.

POSTDOCTORAL POSITIONS
Prostate Cancer

An excellent opportunity for career development to instructor and junior faculty appointment, the position will study the development and growth of prostate cancer using mouse prostate stem cell models. Focus will be on the role of the Pim protein kinase and regulation of TOR. Individuals should have a strong background in transgenic/knockout mouse models and molecular biology/protein chemistry. Forward curriculum vitae and the name of three references to: **Andrew S. Kraft, M.D., Director Hollings Cancer Center, 86 Johnathan Lucas Street, P.O. Box 250955, Charleston, SC 29425. E-mail: hccjobs@musc.edu.** Please reference ad #5001.

POSTDOCTORAL RESEARCH POSITIONS at the Mayo Clinic are available for the following projects: (1) genetic studies of novel breast and ovarian cancer tumor suppressor genes, (2) identification of genetic modifiers of breast cancer risk through gene association studies, and (3) functional studies of novel oncogenes involved in regulation of mitotic integrity. Candidates with a Ph.D. or M.D./Ph.D. degree should send curriculum vitae, summary of research accomplishments, and three letters of reference to: **Drs. C. Szabo and F. Couch, Mayo Clinic College of Medicine, 200 First Street S.W., Rochester, MN 55905 (e-mail: scott.jennifer@mayo.edu).** *Mayo Clinic is an Affirmative Action and Equal Opportunity Employer and Educator.*

POSTDOCTORAL OPPORTUNITIES

POSTDOCTORAL FELLOWSHIP POSITIONS
Available in
The Harvard Reproductive Endocrine Sciences Center, Boston, Massachusetts

The Harvard Reproductive Endocrine Sciences Center is seeking outstanding Postdoctoral Research Fellows with a primary interest in an academic career in the scientific area of the neuroendocrine and genetic control of reproduction. Competitive candidates should: (a) *be U.S. citizens (or have achieved Permanent Resident Status, i.e. have a green card);* (b) have an M.D., Ph.D., or M.D./Ph.D. degree; (c) be seeking an academic career; (d) have an interest in translational investigation; and (e) be familiar with the contemporary investigative tools of genetics, molecular biology, physiology, structural biology, and human/animal investigation. Minorities and women are especially encouraged to apply.

Appropriate candidates should send their curriculum vitae to:

Dr. William Crowley
Center Director
Harvard Reproductive Endocrine Sciences Center
Bartlett Hall Extension 5
55 Fruit Street
Massachusetts General Hospital
Boston, MA 02114
E-mail: crowley.william@mgh.harvard.edu

CANCER RESEARCH

There is an opening for an experienced, highly motivated **POSTDOCTORAL FELLOW** in cancer research. Projects that utilize genetically engineered mouse models, primary cell culture, molecular biology, and biochemistry to characterize novel genes/proteins and their role in tumor development are available (see *EMBO J.* **22(6):**1442, 2003; *J. Biol. Chem.* **280(19):**18771, 2005; *Oncogene* **25(26):**3708, 2006). Applicants must have experience in molecular biology, biochemistry, and cell biology techniques and be willing to work with mice. Applicants must have a recent Ph.D. in a biological science and published evidence of productivity. Interested individuals should send curriculum vitae, a brief statement of research interests and goals, and contact information for three references to: **Dr. Christine Eischen, Vanderbilt University School of Medicine, Department of Pathology, 1161 21st Avenue S. C3322-MCN, Nashville, TN 37232-2561. E-mail: christine.eischen@vanderbilt.edu.** *Vanderbilt University is an Equal Opportunity/Affirmative Action Employer.*

POSTDOCTORAL FELLOW
Johns Hopkins University School of Medicine

Position is within the Department of Radiology and Institute for Cell Engineering. Candidate has strong background in cell biology, biomaterials, and/or biomedical engineering for an NIH-funded RO1 position. Will use magnetically encapsulated islet cells and hepatocytes with image guided techniques for treatment of diabetes and liver failure in mice and swine. Capsules will be tracked with MR imaging. Expertise with biomaterials, cell cultures, immunohistology, and animal surgery a must. Imaging experience is desirable but not required.

Contact: **Dr. Jeff W.M. Bulte, Director of Cellular Imaging; e-mail: jwmbulte@mri.jhu.edu; website: http://www.hopkins-ice.org/vascular/int/bulte.html.**

POSTDOCTORAL SCHOLAR

This position will study cellular and biochemical aspects of G protein-coupled receptor regulation by Ikaros in primary and transduced T lymphocytes. Proficiency in lentiviral transduction, confocal microscopy, and tissue culture is preferred. Please send curriculum vitae and three letters of reference by September 15, 2007, to: **Glenn Dorsam, Ph.D., North Dakota State University, Department of Chemistry, Biochemistry, and Molecular Biology, 320 I.A.C.C., P.O. Box 5164, Fargo, ND 58105. E-mail: glenn.dorsam@ndsu.edu.**

POSTDOCTORAL OPPORTUNITIES

UNIVERSITY CORPORATION for ATMOSPHERIC RESEARCH
Visiting Scientist Programs
Website: http://www.vsp.ucar.edu

Research and training opportunities available for **POSTDOCTORAL FELLOWS** to experienced scientists in the atmospheric, oceanic, and related sciences. University Corporation for Atmospheric Research (UCAR), Boulder, Colorado.

POSTDOCTORAL FELLOW
Johns Hopkins University School of Medicine

Position is within the Department of Radiology and Institute for Cell Engineering. Candidate has strong background in experimental neuroscience and stem cell biology for a position funded by the Maryland State Stem Cell Fund. Will use human embryonic stem cells for treatment of multiple sclerosis in mouse experimental allergic encephalomyelitis models, with MR and bioluminescent imaging to track cells noninvasively. Expertise with neurosurgery, histology, and stem cell cultures a must. Although desirable, imaging experience not required.

Contact: **Dr. Jeff W.M. Bulte, Director of Cellular Imaging, Johns Hopkins University School of Medicine; e-mail: jwmbulte@mri.jhu.edu; website: http://www.hopkins-ice.org/vascular/int/bulte.html.**

POSTDOCTORAL POSITION. This Laboratory is interested in hiring a Postdoctoral Fellow with a deep interest in all aspects of cardiac regeneration: cell biology, molecular biology skills are a must, and applicants with either Ph.D., M.D., or M.D./Ph.D. are sought. Our projects are designed with both mechanistic and translational approaches. We are studying proliferative mechanisms of endogenous cardiac progenitor cells, as well as mechanisms of gene silencing of key cell cycle regulators. Please send or e-mail your resume and contact information for at least three references to: **Dr. Hina W. Chaudhry, Department of Medicine, Division of Cardiology, Columbia University College of Physicians and Surgeons, 622 West 168th Street, PH10-408a, New York, NY 10032 (e-mail: hwc7@columbia.edu).** *Columbia University is an Equal Opportunity Employer.*

POSTDOCTORAL FELLOW or RESEARCH ASSOCIATE to study the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) chloride channel that is implicated in cystic fibrosis and secretory diarrhea. Current projects include: (i) structure-function analysis of CFTR channel regulation and (ii) development of mouse knock-out/knock-in models to explore the functional relevance of protein-protein interactions involving CFTR. Expertise in patch clamping or mouse genetics preferred. Highly motivated individuals will have the opportunity to learn new techniques and to submit independent grant proposals. Contact: **Kevin L. Kirk, Ph.D., Department of Physiology and Biophysics, University of Alabama at Birmingham, 982B MCLM, Birmingham, AL 35294-0005. E-mail: klkirk@uab.edu.** *The University of Alabama at Birmingham is an Affirmative Action/Equal Opportunity Employer.*

DERMATOLOGY, University of Pennsylvania. Two-year **POSTDOCTORAL POSITIONS** to study desmosomal adhesion/pemphigus and Src-tyrosine kinases/Srcasm in cutaneous carcinogenesis. Cell/molecular biology experience required. For carcinogenesis studies, transgenic/gene deficient mouse experience also required. National Research Service Award and NIH grant funding for qualified applicants. E-mail curriculum vitae to **e-mail: paynea@mail.med.upenn.edu** (pemphigus) or **e-mail: john.seykora@uphs.upenn.edu** (carcinogenesis).

Faculty positions in molecular recognition and bioinformatics

POSITION DESCRIPTION

In year 2 of our multi-year recruiting plan, several positions are available immediately at all ranks in the Schools of Medicine and Biomedical Sciences, Dental Medicine, Arts and Sciences, and Engineering at the State University of New York at Buffalo with concomitant appointment in the Center of Excellence for Bioinformatics and Life Sciences.

Successful candidates will have research interests in Bioinformatics and/or Molecular Recognition, in areas such as computational biology, chemical biology, signal transduction, and analysis of biological networks using experimental approaches ranging from in silico through in vivo, and will receive tenured or tenure-track appointments in departments appropriate to their interests. These include, but are not limited to, Biochemistry, Biological Sciences, Chemical and Biological Engineering, Chemistry, Microbiology and Immunology, Oral Biology, Pharmacology and Toxicology, Physiology and Biophysics, and Structural Biology. A history of collaborative research will be a key consideration in evaluation of applicants for senior positions, as will their potential to provide academic leadership.

Additional information on departmental programs may be obtained on specific home pages, accessible via **www.buffalo.edu** or at **www.bioinformatics.buffalo.edu**.

The University at Buffalo is an Equal Opportunity/ Affirmative Action Employer/Recruiter.

STATE-OF-THE-ART FACILITIES

Ample laboratory space exists within all participating departments as well as in the new Center of Excellence building, which opened in June 2006 and is situated adjacent to the Hauptman-Woodward Institute for Structural Biology and the Roswell Park Cancer Institute in the Buffalo-Niagara Medical Campus. The Center maintains a modern, state-of-the-art experimental infrastructure in biomedical sciences, and houses major computational facilities and a high quality confocal microscopy. Cutting edge genomics and proteomics facilities are located within and adjacent to the Center, as well as on the two local campuses of the University at Buffalo.

CANDIDATE REQUIREMENTS

Positions are available at all academic ranks. For senior candidates, a well-established research program is essential. Applicants at the Assistant Professor level should have Ph.D., M.D., D.V.M., D.D.S., or equivalent degree with appropriate postdoctoral and professional experience. Research experience should be in molecular, cellular, chemical, genetic and/or computational approaches to signaling networks, molecular/microbial pathogenesis, development and differentiation or the basis of human disease.

APPLICATIONS

Applications as a single pdf file shall include a C.V., brief statement of research interests, and the names and email addresses of 3 references, and be submitted at **http://www.ubjobs.buffalo.edu**, (posting 0601624) no later than November 1 to receive full consideration.

University at Buffalo *The State University of New York*

UNIVERSITY OF MICHIGAN

SCHOLARS PROGRAMS

BIOLOGICAL SCIENCES SCHOLARS PROGRAM
For Junior, Tenure-Track Faculty

The University of Michigan announces recruitment for the Biological Sciences Scholars Program (BSSP) to continue to enhance its investigational strengths in the life sciences research programs.

Now entering its 11th year, this Program has led to the recruitment of outstanding young scientists in the areas of genetics, microbiology, immunology, virology, structural biology, pharmacology, biocheistry, molecular pharmacology, stem cell biology, physiology, cell and developmental biology, and the neuosciences. The Program seeks individuals with PhD, MD, or MD/PhD degrees, at least two years of postdoccoral research experience, and evidence of superlative scientific accomplishment and scholarly promise. Successful candidates will be expected to establish a vigorous, externally-funded research program, and to become leaders in departmental and program activities, including teaching at the medical, graduate, and/or undergraduate levels. Primary college and department affiliation will be determined by the applicant's qualifications and by relevance of the applicant's research program to departmental initiatives and focus. All faculty recruited via the BSSP will be appointed at the Assistant Professor level.

APPLICATION INSTRUCTIONS: Please apply to the Scholars Programs through the BSSP web site at: (http://www.med.umich.edu/medschool/orgs/bssp). A curriculum vitae (including bibliography), a three-page research plan, an NIH biosketch, and three original letters of support should all be submitted through the BSSP web site. More information about the Scholars Programs, instructions for applicants and those submitting letters of recommendation, and how to contact us is located on the BSSP web site: (http://www.med.umich.edu/medschool/orgs/ssphome/). The final deadline for applications is Friday, October 19, 2007, 5:00 pm EDT.

The University of Michigan is an Affirmative Action/Equal Opportunity Employer.

Director, Center for Biomedical Informatics
National Heart, Lung, and Blood Institute
Department of Health and Human Services
National Institutes of Health (NIH)

The National Heart, Lung, and Blood Institute (NHLBI) at the National institutes of Health (NIH) is seeking a strategic-minded scientist with expertise in research informatics and information technology who will bring significant experience in a research environment to operate in an intellectually challenging Federal biomedical research institution engaged in a national research program to understand, treat, and prevent heart, lung, and blood diseases and sleep disorders throughout the world.

This position offers a unique and challenging opportunity for the right individual to work directly with the NHLBI director to develop a program in research informatics, incorporating information technology. Applicants should possess an advanced science degree and research experience related to bioinformatics or research informatics. Specifically, the successful candidate should have experience in providing bioinformatics support in the areas of biology, molecular biology and genetics, including the terminology of basic, translational, and clinical research. Additionally, applicants should have sufficient education and experience that will ensure success in managing a professional and technical staff engaged in providing complex and computationally intense modeling and analytics in the areas of bioinformatics, genomics, proteomics and imaging. It is highly desirable for the successful applicant to also have extensive experience in information technology management, encompassing strategic planning, complex organizational structures, technical project management and process transformation. The successful candidate will serve as the Chief, Information Officer for the NHLBI, and will oversee operations systems, data warehouse and management reporting and information security and the day to day operations of staff providing IT infrastructure development and support. Strong leadership qualities, negotiation skills, and exceptional interpersonal skills are imperative.

Application Process: Salary is commensurate with experience and a full package of Civil Service benefits is available including retirement, health and life insurance, long term care insurance, leave and savings plan (401K equivalent). Send your application package including: CV, bibliography, and two letters of recommendation to the National Institutes of Health, attn: Alesha Hopkins, 31 Center Drive, MSC 2490, Bldg 31A, Room 5A16, Bethesda, Maryland, 20892-2490. For further information, please contact Ms. Hopkins by email: hopkinsa@mail.nih.gov or telephone (301) 594-4910. Your application package should be received by September 17, 2007. All information provided by applicants will remain confidential and will only be reviewed by authorized officials of the NHLBI. All information provided by candidates will remain strictly confidential and will not be released outside the NHLBI search process without a signed release from candidates.

The NIH encourages the application and nomination of qualified women, minorities and individuals with disabilities.

HHS and NIH are Equal Opportunity Employers

National **Heart Lung and Blood** Institute

WWW.NIH.GOV

PROGRAM DIRECTOR

We are seeking a creative and resourceful physician or neuroscientist with a strong background in higher-level sensory processing to lead a program of basic and clinical research as a Program Director. Research topics relevant to this program include functional neuroanatomy, neurophysiology, and translational applications of higher-order visual, auditory, sensory, and/or vestibular processing. Additional interest in how these systems are regulated by neuroendocrine, cognitive, and/or motor circuits is considered a plus. Appropriate experience includes clinical, patient-oriented, translational and/or basic neuroscience research in academic or for-profit institutions. The successful candidate will join a group of highly interactive scientists and clinicians directing research programs in all areas of modern neuroscience relevant to neurological disorders. He/she will be expected to evaluate and administer extramural research with the goal of building and implementing a cutting edge sensory systems neuroscience research program. Maintaining active communication with the professional and lay communities as well as program staff from other institutes and agencies is considered an integral part of this appointment. In order to qualify for this career position you should have a Ph.D. and/or M.D. degree in a relevant field of biomedical science and appropriate experience. Physicians may be paid a Physician's Comparability Allowance. A recruitment bonus of up to 25 percent may also be paid. Salary is commensurate with experience and expertise. The salary range is $93,822 - $121,967. Application instructions can be found at the USAJobs Web Site **(http://www.usajobs.gov)**, by searching on Vacancy Announcement for **Health Scientist Administrator GS 14 and 15, respectively: NINDS-07-199509-CR-DE, NINDS-07-205828-CR-DE or Medical Officer, GS 14 and 15, respectively: NINDS-07-205966-DH, NINDS-07-205967-DH**. For further information about the application process, please contact **Sharon Scott (scottsha@mail.nih.gov)** at NIH Human Resources. For information concerning the nature of the job, contact **Dr. Debra Babcock at (301) 496-9965 or e-mail her at dbabcock@ninds.nih.gov**.

Staff Scientist
Section on Biological Chemistry

The National Institute of Diabetes and Digestive and Kidney Diseases, a major research component of the NIH and the Department of Health and Human Services, is recruiting a Staff Scientist. The position will be available in Section on Biological Chemistry (http://intramural.niddk.nih.gov/research/faculty.asp?People_ID=1560).

Applications are invited for a highly motivated individual to work collaboratively in an interdisciplinary group that is defining the biological roles of mucin-type O-linked glycans. The successful candidate will lead efforts to phenotype a number of mouse models that have been created and direct efforts to create additional models to understand the mechanisms by which O-glycans function. A number of relevant core facilities, including those required to generate transgenic and knockout models are available within NIH.

Applicants should have an earned Ph.D., M.D., D.D.S. or equivalent doctoral degree and have at least 6 years of relevant laboratory experience in mouse pathology and genetics, as evidenced by published work. The successful applicant will be encouraged to develop an independent line of inquiry. Initial appointment is for five years with the starting salary range of $79,397 to $162,371 per annum.

Applicants should submit their curriculum vitae, a short description of research interests, and names, addresses and email addresses of three references to:

Dr. Lawrence A. Tabak, Building 31, Room 2C39, 31 Center Drive, MSC 2290, Bethesda, MD 20892-2290, Email: Lawrence.Tabak@nih.gov.

The application deadline is **October 1, 2007**.

Post Doctoral Fellowship
Section on Molecular Structure and Functional Genomics

A postdoctoral position is available in the Section on Molecular Structure and Functional Genomics, National Eye Institute, National Institutes of Health, Bethesda, MD with Dr. Graeme Wistow. Projects include:

- Protein interactions in macular degeneration.
- Functional studies of novel growth-factor related proteins in the eye.
- Structure function studies of crystallins and lens-specific proteins.
- Development of an eye-centric protein microarray.

A broad range of techniques are employed, including yeast 2-hybrid, knockout mice, cDNA microarray, 'Biacore' and laser-scattering spectroscopy and collaborative structural analyses. Benefits include health insurance for the trainee and his/her family and travel to one meeting each year. In addition, the NIH Fellows Committee and the Office of Intramural Training and Education sponsor a wide range of career development and social activities. Applications should be sent to: **graeme@helix.nih.gov**.

TENURE-TRACK POSITION
CELL BIOLOGY OF HOST-PATHOGEN INTERACTIONS
National Institute of Child Health and Human Development

A tenure-track position is available in the Cell Biology and Metabolism Branch (http://eclipse.nichd.nih.gov/nichd/cbmb/index.html), NICHD, NIH, to develop an independent research program on the cell biology of host-pathogen or -symbiont interactions. Pathogens and symbionts of interest include viruses, bacteria, and fungi. Outstanding candidates in other areas of cell biology will also be considered. The CBMB has a tradition of excellence in various areas of eukaryotic and prokaryotic cell biology. Other research groups are headed by Irwin Arias, Juan Bonifacino, Ramanujan Hegde, Mary Lilly, Jennifer Lippincott-Schwartz, and Gisela Storz. The recruitment package includes generous funding, two or three additional positions, and laboratory space on the NIH campus in Bethesda. Candidates must have an MD or PhD. Applications should be sent to groverm@mail.nih.gov and include PDF files of the applicant's CV, bibliography, and two-page statement of research plans. Applicants should have three letters of recommendation sent to the above e-mail address. The application deadline is **November 1, 2007**.

DIRECTOR
Life Sciences Innovation Center

The Medical College of Georgia, located in Augusta, GA has an opening for Director of the Life Sciences Innovation Center. The Director will serve as the primary contact for the life science industry throughout Georgia by providing emerging businesses assistance with financing, planning, and operations; managing the business assistance programs and grant programs; interacting with local and state economic development agencies on behalf of the center and MCG; and managing the daily operations of the Life Sciences Innovation Center and Incubator of Augusta.

Minimum Requirements include:

- Bachelor's Degree from an accredited college or university in Business or related field of study and three years experience
- Knowledge of academia, MCG, the life sciences industry, state resources, entrepreneurship, business incubation, web-based computer searching and intellectual property
- Exceptional management, supervisory, organizational, analytical, planning, interpersonal, listening, observation, and oral/written communication skills
- Ability to work independently, handle confidential information, navigate sensitive situations and resolve issues
- Willingness/ability to travel and valid driver's license

Preferred:

- Master's degree from an accredited college or university
- Experience managing grant-funded programs
- Working knowledge of the life sciences industry in Georgia is highly desirable
- Experience in entrepreneurship or small business

Please see our website **http://www.mcg.edu/Jobs/external.html** for further information.

Director
Gene Targeting and Transgenic Facility

The University of Connecticut Health Center is seeking a Director for its Gene Targeting and Transgenic Facility (**http://gttf.uchc.edu**). This service center has a well-trained technical staff who produce genetically modified mice and provide colony management services for investigators in a dedicated barrier facility. The successful candidate will hold a doctoral level degree and have demonstrated expertise in the design and production of gene targeting constructs, the culture and manipulation of mouse embryonic stem cells, morula aggregation, pronuclei and blastocyst injection, mouse embryo manipulations, line rederivation and cryopreservation. The candidate should have managerial experience and capabilities with computer databases. The successful candidate will have a faculty appointment in an appropriate basic science department.

Candidates should apply electronically by submitting a curriculum vitae and three letters of reference to **Dr. Barbara E. Kream, Chair, Gene Targeting and Transgenic Facility Search Committee** at **gttfsearch@uchc.edu**.

UCHC is an Equal Opportunity Employer M/F/v/PwD.

Baylor University Department of Biology
Animal Physiology Faculty Position

The Department of Biology at Baylor University, Waco, TX, invites applications for a full-time, tenure-track appointment at the Assistant Professor level to begin August 2008. Applicants must have a Ph.D. (or equivalent) and are expected to develop a vibrant, extramurally-funded research program that includes student mentoring. Preference will be given to candidates with a demonstrated ability to examine physiological responses or adaptations of animals.

The Department is committed to excellence in undergraduate and graduate education with an outstanding tradition in basic and applied life sciences. Our graduate programs (Ph.D. and Master's) focus on research in biomedical sciences and in evolutionary/ecological sciences. We seek a candidate to join our significant expansion into a new multidisciplinary science building with outstanding research and teaching facilities (**http://www.baylor.edu/bsb/**). The science building fosters interdisciplinary interactions via a number of institutes and centers, including the Institute for Ecological Earth and Environmental Sciences, Molecular Bioscience Center, Center for Reservoir and Aquatic Systems Research and the Center for Drug Discovery. We seek a scientist who complements our existing interdisciplinary research strengths and who will enthusiastically support our undergraduate and graduate programs. Teaching is expected at the undergraduate level (comparative animal physiology) as well as graduate courses in their area of expertise. Personal research lab space is provided and a competitive start-up package will be negotiated. Additional information regarding the position is available on the departmental web site (**http://www.baylor.edu/biology/**).

Application review will begin **October 15, 2007** and will be accepted until the position is filled. To ensure full consideration, your application must be completed by **November 9, 2007**. To apply, submit application letter, CV, up to three publications, statements of research interest and plans, statement of teaching philosophy, and three reference letters to:

Dr. Robert Doyle, Chair
Department of Biology
One Bear Place 97388
Baylor University, Waco, Texas 76798
Robert_Doyle@baylor.edu

Baylor is a Baptist university affiliated with the Baptist General Convention of Texas. As an Affirmative Action/Equal Employment Opportunity Employer, Baylor encourages minorities, women, veterans, and persons with disabilities to apply.

University of California, Santa Cruz
MICROBE-HOST/ENVIRONMENT INTERACTIONS
Assistant Professor

Seeking outstanding applicants for a tenure track faculty position in **microbe- host/ environment interactions**. The successful candidate will have a strong record of research accomplishments, particularly in the areas of: molecular and cellular host responses to pathogens, including immune responses; microbial interactions with their chemical environment; the effects of toxicants on host-pathogen or microbe-host/environment interactions. Exceptional candidates pursuing innovative research in other areas of environmental health, microbiology, and toxicology may also be considered. Postdoctoral experience is desired. Qualified individuals must be committed to excellence in teaching at both the undergraduate and graduate levels, and be willing to provide service to the University.

For detailed information and application instructions, please refer to **Position #838-08** at **http://www2.ucsc.edu/ahr/academic_employment/Employment_opportunities_bulletin.htm**.

This position is open until filled with initial screening beginning on **November 1, 2007**. To ensure full consideration, all materials must be received on or before that date.

The University of California is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

West Virginia University
ROBERT C. BYRD HEALTH SCIENCES CENTER

Associate Professor or Professor Center for Immunopathology and Microbial Pathogenesis

As part of a major research growth initiative supported by a new **Strategic Research Plan (SRP), West Virginia University Health Sciences Center** is recruiting an outstanding scientist to join the Center for Immunopathology and Microbial Pathogenesis. The Center is one of six interdisciplinary research centers being established in accordance with the **SRP** (*Science*, Sept. 8, vol. 313, p. 1461, 2006). A major goal of this interdisciplinary center is to foster collaborations between basic and clinical investigators at Health Sciences. We are especially interested in scientists with established research programs who have credentials for appointment at the Associate Professor or Professor rank **in the School of Medicine**. Appointee must have transferable NIH-R01 funding and a desire to participate in either graduate and/or health professional education. Health Sciences has seven interdisciplinary Ph.D. programs and a joint M.D/Ph.D. Scholars Program in the biomedical sciences.

The successful candidate will receive a generous startup package, competitive salary and excellent laboratory space. We seek investigators across broad areas of immunology, inflammatory disease or immunopathology who are utilizing molecular biology and/or molecular genetic approaches in their research. Collaborative efforts with other basic scientists as well as physician-scientists at the Health Sciences Center who are investigating inflammatory bowel diseases, viral mediated chronic respiratory diseases, pathogenesis mediated by biofilms, or inflammatory mediated vascular injury are being encouraged. The candidate's tenure-track faculty appointment will be in a basic science or clinical department. For this specific position, appointment would likely be in the Department of Microbiology, Immunology and Cell Biology or the Department of Biochemistry.

Qualifications: A Ph.D., M.D. or M.D./Ph.D. with significant research accomplishments. Applications should include curriculum vitae, a brief description of research interests and contact information (including e-mail) for three references sent to: **Christopher Cuff, Ph.D., Search Committee Chair, Center for Immunopathology & Microbial Pathogenesis, PO Box 9177, West Virginia University Health Sciences Center, Morgantown, WV 26506-9106**. Review of applications will continue until the position is filled.

West Virginia University is a comprehensive, public Carnegie-designated Research institution, with approximately 23,000 undergraduates plus 5,500 graduate and professional students. The Health Sciences Center located on the university campus includes the Schools of Medicine, Pharmacy, Dentistry and Nursing; each having both health professional as well as graduate training programs. Two new research buildings which collectively provide 200,000 sq ft of additional research space are under construction at Health Sciences to accommodate our research growth agenda. Morgantown has 55,000 residents and is rated as one of the best small towns in the U.S., with affordable housing, excellent schools, a picturesque countryside and many outdoor activities.

West Virginia University is an Affirmative Action/Equal Opportunity Employer.

Reactive Transport Modeller - Hydrothermal Geochemist

CSIRO

CSIRO Exploration and Mining, Kensington WA
$63K - $72K plus Superannuation Reference Number: 2007/611

CSIRO Exploration & Mining aims to achieve advances in the understanding of how and where giant world-class ore deposits are formed. One team, Computational Geoscience for Predictive Discovery, is developing new software to aid exploration geoscientists in the predictive discovery of valuable mineral deposits through the simulation of a wide range of relevant earth processes.

We are seeking a Reactive Transport Modeller/ Hydrothermal Geochemist to help apply (and develop) geochemical software for the simulation of reactive transport processes using process models developed through data compilation, acquisition and analysis of hydrothermal ore systems. The critical skills being sort are an understanding of chemical reactions at high temperatures and pressures, and numerical modelling of fluid flow and reaction in hydrothermal systems. While an understanding of reactive transport is desirable we welcome applications from scientists from other research areas who have a strong desire to learn and contribute to this new research frontier.

For selection documentation and details on how to apply visit **www.csiro.au/careers** or call **1300 301 509**.

hms/CD68100

U.S. Department of Energy
Associate Director
Office of Science for Biological and Environmental Research
Announcement # SES-SC-HQ-014 (kd)

The U.S. Department of Energy's (DOE's) Office of Science is seeking qualified candidates to lead its Biological and Environmental Research (BER) Program. With an annual budget of more than $500 million, the BER Program is the nation's leading program devoted to applications of biology to bio-energy production and use and to environmental remediation. The BER Program supports major research programs in genomics, proteomics, systems biology, and environmental remediation. The Program is also one of the nation's leading contributors to understanding the effects of greenhouse gas emissions, aerosols, and atmospheric particulates on global climate change.

The Director of Biological and Environmental Research is responsible for all strategic program planning in the BER Program; budget formulation and execution; management of the BER office including a federal workforce of more than 30 technical and administrative staff; program integration with other Office of Science activities and with the DOE technology offices; and interagency integration. The position is within the ranks of the U.S. government's Senior Executive Service (SES); members of the SES serve in key positions just below the top Presidential appointees. For more information on the program please go to **http://www.sc.doe.gov/ober/**.

For further information about this position and the instructions on how to apply and submit an application, please go to the following website: **http://jobsearch.usajobs.opm.gov/getjob.asp?JobID=58520806&AVSDM=2007%2D06%2D06+13%3A44%3A02&Logo=0&q=SES-SC-HQ-014+(kd)&FedEmp=N&sort=rv&vw=d&brd=3876&ss=0&FedPub=Y&SUBMIT1.x=47&SUBMIT1.y=18**. To be considered for this position you must apply online. It is important that you follow the instructions as stated on the announcement **SES-SC-HQ-014 (kd)** located at the website above.

Institute for Diabetes, Obesity and Metabolism and the Department of Genetics, Assistant Professor/ Associate Professor Tenure Track

The Institute for Diabetes, Obesity and Metabolism (IDOM) and the Department of Genetics at the University of Pennsylvania School of Medicine seek candidate for an Assistant and/or Associate Professor in the tenure track. Rank commensurate with experience. Applicants must have a M.D., Ph.D. or M.D./Ph.D. and have demonstrated excellent qualifications in Education and Research.

We are particularly interested in individuals doing basic research using new technologies to approach scientific problems relevant to the genetics of diabetes or obesity, who can complement and synergize with existing strengths. To learn more about IDOM and Genetics, visit our websites: **http://www.med.upenn.edu/idom/** and **http://www.med.upenn.edu/genetics**.

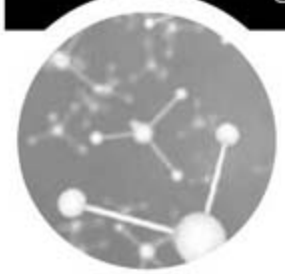
Qualifications and experience in teaching will be required. Independent funding is required for promotion. The successful applicant will receive an excellent start-up package and move into newly renovated space in a superb scientific environment.

Please send curriculum vitae, statement of research interest and three letters of reference to:

Mitchell A. Lazar, M.D., Ph.D.
Professor of Medicine and Chief of Endocrinology, Diabetes and Metabolism
Director, Institute for Diabetes, Obesity and Metabolism
c/o Ms. Vesselina Panteva
University of Pennsylvania School of Medicine
700 Clinical Research Building
415 Curie Boulevard
Philadelphia, PA 19104-6149

The University of Pennsylvania is an Equal Opportunity, Affirmative Action Employer. Women and minority candidates are strongly encouraged to apply.

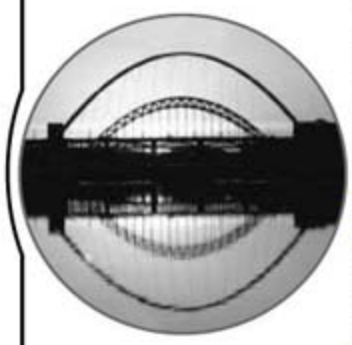
Newcastle.
One of only six Science Cities.
One growing and prosperous region.
One great place to live and work.



Science City Professor/Reader in MEMS

This is an exciting opportunity to develop your career in research, teaching and outreach in areas relevant to the design, manufacture and testing of Micro Electromechanical Systems (MEMS) and microfluidics.

You will need to have achieved international recognition for your research in this area, and demonstrate the potential for leadership. We offer an attractive package of support funding and access to outstanding facilities within a dynamic environment that encourages innovation and enterprise.



Prospective applicants are invited to discuss the post informally with Professor Jim Burdess (j.s.burdess@ncl.ac.uk tel: +44 191 222 6166), or Dr John Appleby (john.appleby@ncl.ac.uk tel: +44 191 222 6286 – Head of School).

For further details of how to apply, please visit our website at www.ncl.ac.uk/sciencecity

Closing date: 28 September 2007.
The post is available from 1 January 2008.

Newcastle Science City
TRANSFORMING TOMORROW

Newcastle University

THE UNIVERSITY of WISCONSIN MADISON

Faculty Position in Physiology

The Department of Physiology, University of Wisconsin School of Medicine and Public Health, invites applications for a tenure-track assistant professor position. Research will focus on aspects of cellular or molecular physiology that reflect emerging trends in the discipline. Successful candidates will demonstrate outstanding research credentials with interests that complement and extend existing focuses in the department (**http://www.physiology.wisc.edu**). The Department is committed to integrative approaches to research problems and especially encourages applications from individuals who employ proteomics, cellular imaging, computational methods, or animal models of human disease. Successful candidates will teach in one or more programs in the Department such as team-taught courses in physiology or our new M.S. in Biotechnology and participate in Ph.D. and post-doctoral training programs. The Department features a breadth of inquiry encompassing molecular to systems level of research, a supportive collegial work environment, and a collective commitment to collaborative research programs. Opportunities for participation in campus-wide interdisciplinary research and training programs are excellent. The successful candidate will also participate in professional, public and university service appropriate to the faculty rank.

Interested individuals should submit curriculum vitae, a one to two page summary of research interests and plans, and three letters of reference to: **University of Wisconsin–Madison, Department of Physiology, Faculty Search Committee #55301, c/o Alice Puchalski, 1300 University Avenue, Madison, WI 53706**, or electronically to **facsearch@physiology.wisc.edu.** To ensure consideration, please submit complete application by **October 31, 2007**. However, applications will be accepted until the position is filled. Unless confidentiality is requested in writing, information regarding applicants and nominees must be released upon request. Finalists cannot be guaranteed confidentiality.

UW-Madison is an Equal Opportunity/Affirmative Action Employer.

Our growth means opportunity for you

Applicants sought for tenure-track positions

Penn State College of Medicine, part of the Penn State Milton S. Hershey Medical Center campus in Hershey, Pennsylvania, announces tenure-track academic research positions across several disciplines. These announcements are part of the College's unprecedented expansion of research facilities and build on a proud history of quality science in a nurturing and collaborative environment.

Research at the College of Medicine is focused on collaboration across departments and campuses and with the community. We encourage partnerships that traverse the research spectrum, from basic study to translational delivery.

To apply, note the code after each job listing and include it in the appropriate spot in the address. Send a curriculum vitae and a statement of research interests to:

Kelly E. Shay
Administrative Assistant, Office of Vice Dean for Research and Graduate Studies (Job code:)
Penn State College of Medicine
500 University Drive, Room C1603, MC: H175
Hershey, PA 17033
or e-mail kshay3@hmc.psu.edu
For more information on positions, visit **www.hmc.psu.edu/college**.

PENNSTATE
Milton S. Hershey Medical Center
College of Medicine

CELLULAR AND MOLECULAR PHYSIOLOGY
- Physiological processes in cells, tissues, and whole animals, esp. in diabetes, obesity, and metabolism (Code: CM1)

MEDICINE

Physician-scientists sought for:
- Metabolic bone disease (Code: DM1)
- Diabetic nephropathy (Code: DM2)
- Virology or immunology (Code: DM3)
- Health care delivery/outcomes research (Code: DM4)
- Hepatology (Code: DM5)

BIOCHEMISTRY AND MOLECULAR BIOLOGY
- Genetics, epigenetics, or genomics, particularly with human or mouse systems (Code: BMB1)
- Expertise in solution NMR, with emphasis on macromolecules or metabolomics (Code: BMB2)

NEUROSURGERY
- Physician-scientists with a specialization in neuro-oncology, functional neurosurgery, or cerebrovascular disease (Two positions; Code: NS1)

NEURAL AND BEHAVIORAL SCIENCES
- Structure, function, or development of the mammalian nervous system (Code: NBS1)

PENN STATE CANCER INSTITUTE
- Hematology/medical oncology, comprising physician-scientists and clinical investigators (Three positions; Code: CI1)
- Molecular epidemiologist (Code: CI2)
- Ph.D. scientist tenure track to run translational research lab (Code: CI3)
- Tenure-track lab position (Code: CI4)
- Benign hematology (Two positions: one junior, one senior; Code: CI5)

PHARMACOLOGY
- Clinical pharmacology (Code: P1)
- Drug discovery (cancer) (Code: P2)
- Graduate/medical education (Code: P3)

PATHOLOGY
- Basic or translational scientists (Two positions; Code PA1) and physician-scientists (Two positions; Code PA1), esp. in cancer, transplantation, lung disease

PUBLIC HEALTH SCIENCES
- Seven positions including health economics, health services research, and cardiovascular epidemiology (Code: PHS1)

U.Ed. MED 6716-08 RES

Penn State is committed to affirmative action, equal opportunity, and the diversity of its workforce. *EOE-AA-M/F/D/V*

TOWSON
UNIVERSITY

CHAIR, DEPARTMENT OF CHEMISTRY
FISHER COLLEGE OF SCIENCE AND MATHEMATICS

Towson University invites applications for the position of Chair of the Department of Chemistry at the rank of full Professor with tenure. The Department is rapidly expanding, ACS accredited, and offers undergraduate degrees in Chemistry, Forensic Chemistry and Medicinal Chemistry, in addition to Masters' degrees in Forensic Science and Chemical Education. The department, which supports interdisciplinary programs in Environmental Science and in Molecular Biology/Bioinformatics/Biochemistry, currently has 16 tenured and tenure track faculty, 6 staff, and approximately 250 Chemistry and Forensic Chemistry majors. Towson University is Maryland's Metropolitan University. Towson enrolls more than 19,000 undergraduate and graduate students in 62 undergraduate majors, 38 masters' programs and four doctoral programs on its attractive campus in suburban Baltimore. The department is housed in The Jess and Mildred Fisher College of Science and Mathematics. The College has been the recipient of several philanthropic gifts and awards which significantly enhance the opportunities of both faculty and students in the college. Candidates must have a Ph.D. in chemistry or a closely related area, and possess excellent leadership, administrative and interpersonal skills, have exemplary professional and research accomplishments, and the ability to attract external funding. The Chair will provide dynamic leadership and promote the department mission within the University and the external community.

Applicants should send curriculum vitae, a statement on the role of the Department Chair, a research plan and the names and addresses of three references to Dr. David Larkin, Chair, Chemistry Chair Search Committee, Office of the Dean, The Jess and Mildred Fisher College of Science and Mathematics, Towson University, 8000 York Road, Towson, MD 21252. Review of applications will begin on October 1, 2007 and continue until the position is filled.

Towson University is an equal opportunity/affirmative action employer and has a strong Institutional commitment to diversity. Women, minorities, persons with disabilities and veterans are encouraged to apply.

PENNSTATE Department of Chemistry

THE PENNSYLVANIA STATE UNIVERSITY
DEPARTMENT OF CHEMISTRY

FACULTY POSITIONS IN ORGANIC CHEMISTRY AND BIOMOLECULAR/ MACROMOLECULAR NMR

Several faculty positions are available for Fall, 2008 at the junior or senior level in the areas of organic chemistry and biomolecular/macromolecular structure and function with an emphasis on NMR spectroscopy. The Chemistry Department has recently moved into a new state-of-the-art building. Departmental research spans both traditional and non-traditional areas. Faculty members have opportunities to participate in university-wide life sciences, materials, environmental, and computational institutes. Appointees are expected to establish an exceptionally strong and highly visible research program that incorporates excellence in undergraduate and graduate education. Senior appointments should have a previous record of national and international distinction.

Applicants should submit curriculum vitae, list of publications, and research plans to: **Chair of the Search Committee, Box C, Department of Chemistry, 104 Chemistry Building, The Pennsylvania State University, University Park, PA 16802**. Junior applicants should also arrange to have three letters of recommendation sent to this address. Review of applications will begin on **October 1, 2007** and continue until the positions are filled.

To view this position:
http://www.chem.psu.edu/faculty/facultyad.html

Penn State is committed to Affirmative Action, Equal Opportunity and the diversity of its workforce.

Minnesota Partnership for Biotechnology and Medical Genomics

UNIVERSITY OF MINNESOTA — MAYO CLINIC

Under the auspices of the **Minnesota Partnership for Biotechnology and Medical Genomics,** the Cancer Centers at the University of Minnesota and the Mayo Clinic are undertaking paired faculty recruitments in the areas of pharmacogenomics and statistical genetics. It is anticipated that these hires will serve as focal points for future research interactions and collaborations between the University of Minnesota and the Mayo Clinic.

Mayo Clinic
Tenure Track Position in Statistical Genetics/Oncology
Pharmacogenomics
Rochester, Minnesota

Mayo Clinic, located in Rochester, Minnesota, is seeking a full-time faculty member, at the Assistant, Associate, or Full Professor level, with broad expertise in biostatistics and a working knowledge of genetics. This is a newly funded position within the Mayo Clinic NCI Comprehensive Cancer Center and the Mayo Clinic NIH Pharmacogenetics Research Network that focuses on the analysis of complex genomic data relevant to understanding the pharmacogenomics of cancer. The successful candidate will be an outstanding investigator with research accomplishments and scholarship in the application of statistical methods to the study of complex genetic diseases and traits. The primary appointment will be in the Division of Biostatistics, which has 28 faculty members, with a secondary appointment in the Division of Oncology. The appointed faculty will join a multidisciplinary community of scientists and clinician-investigators studying the genetic basis of cancer treatment with cutting edge research programs, and an expanding staff in statistical genetics and bioinformatics.

Minimum qualifications include a Ph.D. degree in statistics, biostatistics, bioinformatics, or a closely aligned quantitative area, with computational experience, as well as excellent oral and written communication skills. The position includes a generous start-up package with a Mayo core research budget, as well as a competitive compensation and benefits package.

To learn more about Mayo Clinic and Rochester, MN, please visit **www.mayoclinic.org**.

Applicants should submit their curriculum vitae with a cover letter summarizing their research background, interests, and goals, representative publications, as well as three letters of recommendation, sent separately. Review of applications will begin **September 1, 2007**, and will continue until the position is filled. Material should be submitted to: **Daniel J. Schaid, Ph.D., Harwick 7, Mayo Clinic, 200 First Street, S.W., Rochester, MN 55905; Email: searchsgen@mayo.edu; Phone: (507) 284-0639.**

Mayo Foundation is an Affirmative Action and Equal Opportunity Educator and Employer.
Post offer/pre-employment drug screening is required.

ChemGen IGERT

The **University of California, Riverside** seeks qualified domestic PhD students in biological sciences, chemistry, computer science and chemical engineering to participate in an innovative graduate training program that melds science and technology through chemical genomics research. Fellowships offer interdisciplinary research training that applies chemical biology and chemical genomics to study plant cells and model plant pathogens.

Fellowships include interdisciplinary graduate training with cross-disciplinary coursework and research rotations, internships, travel and research support. Fellows receive 5 years of funding including 2 yrs of National Science Founation stipend at $30K/yr (**www.cepceb.ucr.edu/IGERT/IGERT.htm**).

Faculty mentors, state-of-the-art research opportunities, student projects, and application instructions are described on the Center for Plant Cell Biology website (**www.cepceb.ucr.edu**).

Participating Graduate programs include: Plant Biology, Genetics, Genomics and Bioinformatics; Cell, Molecular and Developmental Biology; Biochemistry and Molecular Biology; Chemistry; Computer Science and Engineering; Chemical and Environmental Engineering.

Minnesota Partnership for Biotechnology and Medical Genomics

UNIVERSITY OF MINNESOTA — MAYO CLINIC

Under the auspices of the **Minnesota Partnership for Biotechnology and Medical Genomics**, the Cancer Centers at the University of Minnesota and the Mayo Clinic are undertaking paired faculty recruitments in the areas of pharmacogenomics and statistical genetics. It is anticipated that these hires will serve as focal points for future research interactions and collaborations between the University of Minnesota and the Mayo Clinic.

University of Minnesota
Faculty Position in Pharmacogenomics/Bioinformatics

The Medical School and College of Pharmacy invite applications from outstanding candidates for a tenure track or tenured position. All academic ranks will be considered. The School seeks applicants with a Ph.D. or PharmD, and evidence of an independent, nationally recognized, funded research program in pharmacogenomics, with a particular emphasis on cancer therapeutics. The candidate will be expected to develop research leadership in an interactive, interdisciplinary program of medical genomics in the Academic Health Center and the Cancer Center, with access to strong facilities in genomics, informatics, drug screening, medical genetics, and pharmacology within NCI Comprehensive Cancer Centers at the University and Mayo Clinic. The departmental appointment will be according to the candidate's interests and programmatic fit.

To apply, please go to **http://employment.umn.edu**, search for **Job Requisition #148688** for application instructions and links. All applications must be submitted on line, and should include names of references. Review of completed applications will begin **September 1, 2007**, and will continue until the position is filled. For questions regarding this position, contact **Dr. Brian Van Ness** at **612-624-9944 (vanne001@umn.edu)**, or **Dr. Tim Tracy** at **612-625-7665 (tracy017@umn.edu)**.

The University of Minnesota is an Equal Opportunity Educator and Employer.

Director, MDI Biological Laboratory

The Mount Desert Island Biological Laboratory (MDIBL), located on Mt. Desert Island, Maine, home of Acadia National Park, is a 109 year-old independent research institution. The Laboratory is known for its world-class seasonal scientific and educational programs, and an expanding year-round research program, that focus on marine physiology, epithelial transport, developmental biology and environmental toxicology.

MDIBL invites applications for the Position of Scientific Director. He/she will be responsible for articulating the scientific vision and overseeing the development, implementation, execution, and management of the scientific and educational agenda of the Laboratory. The Director, who reports to the Board of Trustees, serves as Chief Executive of the Institution to whom the senior administrative staff and year round investigators report. The candidate must be a seasoned, grant-supported academic scientist and administrator. Experience interacting with basic marine biologists, physiologists, biomedical investigators and/or environmental toxicologists is advantageous. Effective communication and interpersonal skills as well as successful dealings with private donors and government officials at all levels are important prerequisites for this position.

Please send a letter of interest, CV, and the names and addresses of three references to: **Search Committee, MDIBL, Box 35, Salisbury Cove, ME 04672 or search_committee@mdibl.org**. A detailed job description can be found at: **www.mdibl.org/info/careers.shtml.** Review of applications will begin October 15.

MDI Biological Lab

MDI Biological Laboratory is an Affirmative Action/Equal Opportunity Employer. Women and members of minority groups are encouraged to apply.

お茶の水女子大学
Ochanomizu University

Nine Tenure-Track Assistant Professor Positions

GRANT TO PROMOTE YOUNG SCIENTISTS' INDEPENDENT RESEARCH

Outline:
Ochanomizu University, a National University Corporation in Japan, invites applications for full-time appointments at the Assistant Professor level as a program-specific fixed-term faculty member in the following prioritized research fields. This program is supported by the Special Coordination Funds for Promoting Science and Technology commissioned by the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Research fields:
(A) Bioinformatics, (B) Quantum Information Science, (C) Simulation Science, (D) Soft-Matter Science, (E) Supramolecular Chemistry, (F) Ubiquitous Computing, and related basic and applied sciences.

Qualifications:
Candidates should hold Ph.D. degrees granted within the past 10 years (as of August 1, 2007), and have outstanding research experience and excellent ability to perform creative and independent research.

Term:
The initial appointment will start from early December, 2007 (at the earliest) to March 31, 2009. The term will be extended to March 31, 2012, based on the interim assessment of the research record. Pending the final assessment within the 5th year, the successful candidates will be tenured.

For details, please visit the following website:
http://www.cf.ocha.ac.jp/acpro/

Deadline for applications: October 1, 2007
Address for submitting the application:
Applicants should send application documents by registered mail to
President Mitiko Go, Ph.D.
Ochanomizu University
2-1-1 Otsuka, Bunkyo-ku, Tokyo 112-8610, JAPAN.

On the envelope, please write "Application for Assistant Professor" in red.

For further inquiries, please e-mail to **acpro@cc.ocha.ac.jp** or fax to +81-3-5978-5648.

Western University
OF HEALTH SCIENCES

The discipline of learning. The art of caring.

Applications are invited to fill two TENURE-TRACK POSITIONS in the Department of Pharmaceutical Sciences, College of Pharmacy, Western University of Health Sciences (website: **http://www.westernu.edu/**). Rank and salary are commensurate with qualifications and experience.

Candidates must be highly motivated to excel in teaching in the professional Pharmacy (Pharm.D.) Program and possess a Ph.D. in pharmacology or a closely related field with postdoctoral training. The candidates will also be expected to teach in our Master's program. Individuals with previous teaching experience, especially in nervous system or cardiovascular pharmacology, endocrinology or cancer chemotherapy, are encouraged to apply. In addition, the successful candidates are expected to establish an independent extramurally funded research program. Research startup funds are available.

The review of applicants will begin immediately and continue until the positions are filled. The salary is competitive, and the starting date is September 1, 2007. To be considered for this position, applicants should submit a letter of intent, curriculum vitae, teaching/research statement, and arrange to have three letters of references sent (e-mail preferred) to: **Dr. Kabir Lutfy, Chair, Search Committee, Department of Pharmaceutical Sciences, College of Pharmacy, Western University of Health Sciences, 309 East Second Street, Pomona, CA 91766 (e-mail: klutfy@westernu.edu)**.

Medical College of Georgia
Department of Physiology
Faculty Positions in Cardiovascular, Endocrine, and Renal Physiology

The Department of Physiology invites applications for three tenure-track positions. The rank of the appointment (Assistant Professor/Associate Professor/Professor) will be commensurate with the qualifications and experience of the successful candidate. A degree in medicine, veterinary medicine, or Ph.D. in biological sciences with postdoctoral research experience is required. Successful candidates are expected to establish active independent programs of extramurally funded research to complement research strengths and goals of the department and the medical college. Our department focuses on questions of cellular signaling, neural regulation, and hormonal control in a broad range of model systems of cardiovascular, endocrine, and renal disease. Successful candidates will receive substantial start-up packages and be housed in newly constructed/renovated facilities. There is a strong institutional commitment to core facilities, graduate programs, and an interdisciplinary approach. Applicants are also expected to have teaching experience and be committed to teaching students in the schools of medicine and graduate studies.

Applicants should submit a curriculum vitae, a statement of research interests and career goals, and three letters of reference to **ASchreihofer@mcg.edu** or by mail to:

Ann M. Schreihofer, Ph.D.
Search Committee Chair
Department of Physiology
1120 15th Street
Medical College of Georgia
Augusta, GA 30912-3000

For full consideration, applications should be received by **September 30, 2007**. Visit us at **http://www.mcg.edu/som/phy/**.

The Medical College of Georgia is an Equal Opportunity and Equal Access Institution.

The University of Texas at Austin

Eukaryotic Molecular Biology Positions

The Institute for Cellular and Molecular Biology

The Institute for Cellular and Molecular Biology, Alan Lambowitz, Director, invites applications for two tenure-track/tenured positions in eukaryotic molecular biology. Academic appointments at the level of Assistant, Associate, or Full Professor will be in an appropriate academic unit in the College of Natural Sciences. Candidates should have an outstanding record of research productivity and a research plan that utilizes molecular and biochemical approaches to address important problems in eukaryotic molecular biology. Areas of particular interest include but are not limited to chromatin structure, regulation of gene expression, microRNAs and RNA interference, DNA damage responses, and cell cycle control.

Building on a strong existing faculty, the Institute has recruited more than 45 new faculty members over the past nine years (see www.icmb.utexas.edu). In addition to it's highly interactive and interdisciplinary research environment, the Institute provides administrative and financial support for the Graduate Program in Cell and Molecular Biology and state-of-the-art core facilities including DNA sequencing, mass spectrometry, electron and confocal microscopy, DNA microarrays, robotics, and mouse genetic engineering. A recently instituted MD-PhD program with the UT Medical Branch and the new Dell Pediatrics Research Institute further enhance the environment for basic Biomedical Research.

Austin is located in the Texas hill country and is widely recognized as one of America's most beautiful and livable cities.

Please apply on-line at http://www.icmb.utexas.edu/apply/between Sept. 1 and Nov. 1, 2007.

The University of Texas at Austin is an Equal Opportunity Employer. Qualified women and minorities are encouraged to apply; a background check will be conducted on applicant selected.

The Asia Pacific Center for Theoretical Physics (APC•TP), Korea and the Max-Planck-Gesellschaft (MPG), Germany

are seeking outstanding candidates for

Two leaders of Independent Junior Research Groups in Theoretical Physics

The rules for MPG Independent Junior Research Groups apply to the selection process. The two groups will be located on the campus of Pohang University of Science and Technology (POSTECH). The fields of research envisaged are

- Multiscale modeling (e.g., ab initio electronic structure theory especially based on wavefunction methods, embedding, microstructures, shape memory materials)
- Modern field theoretical methods in condensed matter physics (e.g., topological order, gauge theories, fractionalization, entanglement)

The two groups will strengthen the scientific in-house program of the APC•TP. The Center has twelve membership countries and is serving their physics communities by organizing schools, workshops, training programs etc. Strong links exist to the Physics Department of POSTECH. The group leaders are expected to use also the links to renown research centers in the Asia Pacific region to which the APC•TP has close relations.

We offer positions for 5 years on a salary which corresponds to an exceptional Assistant Professor. Funds are available for 1 – 2 postdoctoral fellows, 1 – 2 guests and 1 – 2 PHD students for each group which shall be recruited by the group leaders. We will provide office and adequate funds for computer access and consumables.

Please send your CV, publication list and a short description of your research accomplishments and future plans to Prof. Seunghwan Kim at the address below by October 15, 2007. Two letters of recommendation should be sent separately by the application deadline.

Asia Pacific Center for Theoretical Physics
Hogil Kim Memorial Bldg. #501, POSTECH
San 31 Hyoja-dong, Nam-gu, Pohang
Gyeongbuk 790-784, KOREA
email: sec@apctp.org

APCTP

University of Central Florida

UCF COLLEGE OF MEDICINE FOUNDING FACULTY

The University of Central Florida College of Medicine invites applications from educators, clinicians, and researchers for faculty positions at all ranks to develop, teach, coordinate, anchor, and administer an integrated, organ system-based curriculum for medical students in basic sciences, clinical sciences, and other areas of medical education, including informatics, ethics, biostatistics, public health, and others. The college expects to admit its charter class as early as fall 2009 pending preliminary accreditation by the LCME. Founding faculty members will focus on creating the new M.D. curriculum with a strong clinical basis.

Candidates must have a doctoral level degree and a minimum of three years of experience in an M.D., biomedical, or related educational program. For administrative positions, candidates should have significant leadership experience in the discipline or practice of medicine. Excellent communication, organizational, and interpersonal skills and evidence of teaching excellence are important.

The application should include a letter of interest addressing the applicant's qualifications for developing and teaching an integrated M.D. curriculum, curriculum vitae, and names of three references. Review of applications will commence immediately and continue until positions are filled. Search materials are available for public review as provided by Florida statute. Send application material to: **Search Manager, College of Medicine—Faculty Search Committee, University of Central Florida, P.O. Box 160116, Orlando, Florida 32816-0116 (407) 823-4073;** email: **nknobbs@mail.ucf.edu**. Visit COM Website at **http://med.ucf.edu**.

UCF is an Equal Opportunity/Affirmative Action Employer.

Featured Employers

Search **ScienceCareers.org** for job postings from these employers. Listings updated three times a week.

Abbott Laboratories www.abbott.com

Amgen www.amgen.com

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Genentech www.gene.com

Invitrogen www.invitrogen.com/careers

Kelly Scientific Resources
www.kellyscientific.com

Novartis Institutes for BioMedical Research
www.nibr.novartis.com

Pfizer Inc.
www.pfizer.com

Philip Morris
www.cantbeattheexperience.com

Pioneer Hi-Bred
www.pioneer.com

If you would like to be a featured employer, call 202-326-6543.

Science Careers
From the journal *Science* AAAS

The University of North Dakota
School of Medicine & Health Sciences
501 N. Columbia Road Stop 9037
Grand Forks, ND 58202

UND

Associate Dean for Research

Applications are invited for an accomplished senior investigator to fill the position of Associate Dean for Research with an appointment as Professor/Associate Professor in a suitable research-focused academic department. The School of Medicine and Health Sciences at the University of North Dakota has excellent space, state-of-the-art equipment, and a young and ambitious faculty who receive over $20M per year in extramural support for their research activities. The successful candidate will be expected to maintain an active extramurally-funded research program, participate in graduate and medical education, and provide creative leadership and guidance to develop, promote, and sustain an increased culture of research excellence and productivity within the School of Medicine and Health Sciences. Applications will be reviewed as received and the position will remain open until filled.

Please send current curriculum vitae, contact information for at least three individuals willing to serve as references, and descriptions of administrative, research, teaching and service activities to **Dr. Jonathan D. Geiger, Professor and Chair, Department of Pharmacology, Physiology and Therapeutics, Box 9037, University of North Dakota, School of Medicine and Health Sciences, Grand Forks, ND 58203 (Ph. 701-777-2183, Fax 701-777-4490, jgeiger@medicine.nodak.edu)**. The University of North Dakota, with about 13,500 students, is located in Grand Forks, ND, a family-orientated community of over 50,000 people with excellent schools, parks, and abundant year-round outdoor recreational activities.

The University of North Dakota is an Equal Opportunity/Affirmative Action Employer and invites applications from all qualified individuals.

www.med.und.nodak.edu

Idaho National Laboratory
DIRECTOR
Center for Advanced Modeling and Simulation

The Idaho National Laboratory (INL) is seeking a Director for the Center for Advanced Modeling and Simulation (CAMS). Preferred candidates will have a PhD in engineering science, physical science, applied mathematics or computer science, at least fifteen years post-PhD experience, a strong record of research accomplishment and management experience. The position also requires well-developed leadership, planning, execution and interpersonal skills. The CAMS Director works with management and staff in the INL Mission Accomplishment Directorates and Information Technologies Directorate to ensure that INL has the computational capabilities (including highly skilled staff) needed to support its major missions in Nuclear Science and Technology, National and Homeland Security Science and Technology and Energy and Environmental Science and Technology. He/she is also responsible for strengthening the INL computational science and engineering community and fostering productive partnerships with universities, other government laboratories and the private sector. Preference will be given to candidates who can demonstrate a strong commitment to cross-disciplinary intra-institutional and inter-institutional collaboration. The successful candidate will be encouraged, but not required, to maintain an active research program.

INL is a science-based, applied engineering national laboratory. It is operated for the Department of Energy by Battelle Energy Alliance and partners.

Applicants should submit a current CV including a list of publications to: **Paul Meakin, Laboratory Fellow and Director of the Center for Advanced Modeling and Simulation, Idaho National Laboratory, P.O. Box 1625, Mail Stop 2211, Idaho Falls, ID 83415-2211**. Candidates should arrange for at least six letters of recommendation to be sent to **Paul.Meakin@inl.gov** or contact information for the references should be included in the CV. Evaluation of applications will begin on **September 15, 2007** and applications will be accepted until the positions are filled. INL is an

Equal Opportunity Employer M/F/D/V.

VA NORTH TEXAS HEALTH CARE SYSTEM

COMPASSION, EXCELLENCE, AND DEDICATION
TO OUR NATION'S VETERANS!

ASSOCIATE CHIEF OF STAFF FOR RESEARCH AND DEVELOPMENT

VA North Texas Health Care System (VANTHCS) is recruiting a full time Associate Chief of Staff for Research and Development at the Dallas VA Medical Center. This institution is one of the major teaching hospitals of the University of Texas Southwestern (UTSW) Medical School and is the fifth busiest VA system in the nation. Accordingly, the candidate must be eligible for a tenured appointment at a rank not less than an Associate Professor level. The successful candidate will maintain the institution's existing strengths in funded basic and clinical research, and further develop the R & D program with a focus on expanding translational, patient centered, and HSR & D research at the institution. We are seeking a candidate who will maintain and strengthen the collaboration between VANTHCS and our affiliate.

VANTHCS is seeking a dynamic professional to join an organization with an excellent staff of academic faculty and experienced medical professionals. The candidate preferably has a successful track record in translational-clinical or HSR& D research and possesses a history with a sustained, independent research program. Recent successful research history is preferred. For clinician-scientists, clinical responsibilities and service assignments are negotiable.

The Dallas facility is part of an integrated health care system located in a cosmopolitan city with numerous social and cultural opportunities.

Qualifications Include:

- Must be a U.S. Citizen and possess an active medical license to practice in a state, territory or commonwealth of the U.S. or in the District of Columbia.
- Academic rank will be commensurate with experience and will be determined by the affiliate institution.

The VA offers excellent benefits in a professional and rewarding environment. Benefits include: 26 vacation days, 13 sick leave days per year/accumulates without limit, 10 paid holidays, generous retirement package including 401K savings plan with employer matching contributions, malpractice insurance paid by VA, health and life insurance benefits, free parking, wellness center, and tax free retail store.

Candidates should forward their Curriculum Vitae, statement of professional goals and three references to:

Al Richard
Physician Recruiter (05)
4500 S. Lancaster Road
Dallas, TX 75216
AlcintiaD.Richard@va.gov
(214) 857-1685

VA NORTH TEXAS HEALTH CARE SYSTEM

4500 S. Lancaster Road | Dallas, TX 75216 | Located on the Dart Rail Line
U.S. Citizenship Required. Applicants Subject to Drug Testing.

POSTDOCTORAL OPPORTUNITIES

The Diabetes Institute for Immunology and Transplantation (DIIT) in the Department of Surgery at the University of Minnesota (U of M) is recruiting a **POSTDOCTORAL FELLOW** with expertise in magnetic resonance spectroscopy and imaging with preferred experience in the study of biological, medical, and/or tissue engineering applications.

The applicant must hold a Ph.D. in biophysical sciences, biomedical engineering, or related field and have demonstrated success as an independent researcher with associated publications. Experience on a Siemens and/or Varian platform, familiarity and 19 F nuclear magnetic resonance (NMR) spectroscopy and imaging preferred. Responsibilities will include facilitating, coordinating and conducting multidisciplinary collaborative research between the DIIT and the U of M Center for Magnetic Resonance Research (CMRR) as well as the Center for Interdisciplinary Applications of Magnetic Resonance (CIA MR) facility. Research will focus on developing technology and methods for noninvasive assessment of the anatomic, functional and metabolic aspects of pancreatic islet cells in vitro and in vivo, support the study of novel surgical interventions being developed to facilitate islet transplantation for type 1 diabetics. In vivo research will focus on developing non-invasive methods to evaluate the disposition, oxygenation and viability of transplanted pancreatic islet cells in a surgically engineered environment. In vitro work with 13 C and 31 P NMR spectroscopy will involve studies of islet metabolism under conditions encountered pre and post-transplantation to develop interventional strategies for increasing transplantation success rates. The position will report to the Director of Islet Processing Research and Development at the DIIT and be co-supervised by collaborating faculty at the CMRR and CIA-NMR. This position is funded for two years, with an opportunity for renewal thereafter.

POSTDOCTORAL POSITION available, through a training cooperative agreement between the Department of Environmental Sciences and Engineering, University of North Carolina, Chapel Hill, and the National Health and Environmental Effects Research Laboratory, U.S. EPA, Research Triangle Park, North Carolina, for a recent Ph.D. with training in mathematical modeling, to conduct extrapolation modeling research directed toward improved methods for extrapolation, based on appropriate metrics of internal dose, across exposure duration, exposure concentration, route and species. *Proof of U.S. citizenship required.* To apply (curriculum vitae plus names of three references) or request information: **Professor L.M. Ball, e-mail: lmball@unc.edu; telephone: 919-966-7306.**

POSTDOCTORAL POSITIONS in immunology are available to study cytokine control of T regulatory cell function and homeostasis. There are also opportunities to investigate T cell memory development in the context of tumor immunity. Description of current research is described at **website: http://chroma.med.miami.edu/micro/faculty_malek.html.** Candidates must have a Ph.D. or M.D. degree. Prior experience in immunology is preferred. Send curriculum vitae, description of research interests, and names of three references by e-mail to: **Dr. Thomas Malek, Department of Microbiology and Immunology, Miller School of Medicine, University of Miami, Florida. E-mail: tmalek@med.miami.edu.**

RESEARCH ASSOCIATE/POSTDOCTORAL POSITIONS available to study negative regulation of signal transduction in antigen presentation and to develop novel immunotherapy against cancer and HIV infection (*Nat. Biotechnol.* **22**:1546, 2004; *J. Clin. Investig.* **116**:90, 2006; *Public Library of Science Medicine* **3**:76-93 e11, 2006). Experience in immunology and molecular biology, especially dendritic cell biology, mouse tumor models, and viral vector is preferred. Send curriculum vitae and three references to: **Dr. Si-Yi Chen (e-mail: siyichen@usc.edu), Keck School of Medicine, University of Southern California, Los Angeles, CA 90033.**

POSITIONS OPEN

PIONEER
A DuPont Company

SENIOR RESEARCH SCIENTIST/ RESEARCH COORDINATOR
Transgenic Agronomic Traits (5666BR)

An experienced Scientist is required to lead a group of researchers responsible for advancing our yield enhancement research and for delivering products that are transgenically enhanced for increased yield and productivity under abiotic stress. The person filling this position also will fill a requirement for leadership in developing the next generation of yield-enhanced crops requiring multiple transgenes and delivering improved performance across a wide variety of environments.

The successful candidate will have a Ph.D. in biological sciences and 10 to 12 years of experience in area of specialty or unique scientific skills. The person in this leadership position will be knowledgeable of the latest techniques and approaches to achieving enhanced, stable yield in crop plants. The individual will evaluate, manage, and coordinate research activities within the yield enhancement group of the Agronomic Traits Department. Outstanding supervisory, management, communication, and interpersonal skills will be essential to success. This person will be expected to work cross functionally both within the Department and across other departments of the Crop Genetics Research and Development organization. An understanding and knowledge of plant breeding is crucial. Knowledge of molecular techniques, approaches, and gene expression is critical.

To learn more about this position and to apply, please go to **website: http://www.pioneer.com/careers.** *Equal Opportunity Employer.*

POSTDOCTORAL OPPORTUNITIES

Several **POSTDOCTORAL POSITIONS** are offered in the **Ozcan** Laboratory in the Division of Endocrinology, Children's Hospital Boston, Harvard Medical School.

Positions are offered to study the role of endoplasmic reticulum stress and unfolded protein response (UPR) signaling and also the effect of chemical chaperones on: (1) Insulin receptor signaling and Type 2 diabetes in obesity, (2) Beta-cell function and homeostasis, (3) Hypothalamic control of metabolic homeostasis (strong neuroscience background is required for the candidates applying for this area of research), (5) Atherosclerosis, and (6) Adipocyte differentiation and adipose tissue metabolism in obesity. The ideal candidates should have a Ph.D., M.D. or M.D./Ph.D. degrees with strong background in molecular biology and genetics evident by peer-reviewed publications in reputable journals.

Interested candidates should forward their research interests and curriculum vitae along with the name and contact information of three references to: **Dr. Umut Ozcan; e-mail: umut.ozcan@childrens.harvard.edu, telephone: 617-919-4684.**

Two **POSTDOCTORAL POSITIONS** are available to study Nrf2 and INrf2 (Keap1) signaling in oxidative stress and cell survival. It involves studying modifications of Nrf2 and INrf2 by serine/threonine and tyrosine kinases and redox factors and generation of knockout/transgenic mice models to study Nrf2 and INrf2 signaling in cell survival and in vivo role in prevention of oxidative stress and related diseases. Experience in biochemical and molecular biology techniques is essential. Applicants should submit curriculum vitae, names, addresses, telephone numbers and e-mail addresses of three references. Contact: **Dr. Anil K. Jaiswal, Ph.D., Professor, Department of Pharmacology, University of Maryland School of Medicine, 655 West Baltimore Street, Baltimore, MD 21201,** or **e-mail: ajaiswal@som.umaryland.edu.** *Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

MATHEMATICAL BIOLOGY FACULTY
Loyola Marymount University

The College of Science and Engineering seeks candidates for a **PRESIDENTIAL PROFESSORSHIP** in mathematical biology. Candidates must have a distinguished record in teaching and research and a clear vision for providing leadership in interdisciplinary educational and research programs in mathematical biology. The ideal candidate will receive a joint appointment in biology and mathematics at the rank of **PROFESSOR,** but exceptional candidates at the rank of **ASSOCIATE PROFESSOR** will also be considered. Our College's faculty have a variety of current and emerging research interests, including bioinformatics, coding theory, dynamics, ecology and evolution, epidemiology, genomics, knot theory, modeling, proteomics, and probability and statistics. The individual we are seeking will broaden and complement our current interests and expertise. Loyola Marymount University currently maintains an individualized studies undergraduate degree in biomathematics, and we are actively developing a formal major. Our College currently participates in two Research Experiences for Undergraduates programs, with more under development. Research programs in mathematical biology and quantitative biology and ecology enjoy support from a variety of sources. Local availability of the Ballona Wetlands as a living laboratory inspires important and innovative interdisciplinary scholarly and instructional pursuits. The successful candidate will provide leadership not only in the undergraduate degree programs and any future initiatives but also the recruitment of additional faculty to strengthen crosscutting interactions among departments in the College.

Requirements for the position include a Ph.D. in biology, mathematics, or a relevant, related discipline. Applicants are requested to send a letter of application, curriculum vitae, vision statement for the position, and three letters of reference. Review of applicants will begin December 3, 2007. Materials should be sent to: **Biomathematics Search Committee, Department of Mathematics, UH 2700, Loyola Marymount University, 1 LMU Drive, Los Angeles, CA 90045-2659.** For additional information, contact **Dr. Ben Fitzpatrick, e-mail: bfitzpatrick@lmu.edu,** or **telephone: 310-338-7892.** To learn more about Loyola Marymount University and the College, visit **websites: http://www.lmu.edu** and **cse.lmu.edu.** *Loyola Marymount, a comprehensive university in the mainstream of American Catholic higher education, seeks professionally outstanding applicants who value its mission and share its commitment to academic excellence, the education of the whole person, and the building of a just society. LMU is an Equal Opportunity Institution actively working to promote an intercultural learning community. Women and minorities are strongly encouraged to apply.*

POSTDOCTORAL OPPORTUNITIES

POSTDOCTORAL POSITIONS. Available for studies in various aspects of toxicology and environmental health in the Center in Molecular Toxicology through the Departments of Biochemistry, Biological Sciences, Chemistry, Medicine, Pathology, Pediatrics, and Pharmacology. Areas of investigation relating to molecular toxicology and environmental health include oxidative damage, DNA damage and genetic instability, maintenance of genomic integrity, enzymatic biotransformation and reactions of electrophiles, and neurotoxicology. Center faculty include **Drs. Richard N. Armstrong, Judy L. Aschner, Michael Aschner, Nancy J. Brown, Raymond F. Burk, Richard M. Caprioli, Walter J. Chazin, David K. Cortez, Martin Egli, Brandt F. Eichman, F. Peter Guengerich, Tina V. Hartert, T. Alp Ikizler, Daniel C. Liebler, Lawrence J. Marnett, Jason D. Morrow, Jennifer A. Pietenpol, Ned A. Porter, Carmelo J. Rizzo, Michael P. Stone, William M. Valentine,** and **Michael R. Waterman.** Salaries are negotiable. Applicants should submit curriculum vitae and three letters of recommendation to: **Dr. F. Peter Guengerich, Director, Center in Molecular Toxicology, Vanderbilt University, School of Medicine, Nashville, TN 37232-0146. Website: http://www.toxicology.mc.vanderbilt.edu.**
An Affirmative Action/Equal Opportunity Employer.

Faculty Positions
Department of Pharmaceutical Sciences
University of Hawaii at Hilo
College of Pharmacy

The University of Hawaii at Hilo invites applicants for faculty positions in their new College of Pharmacy. Each of the positions listed below are immediately available for full-time (11 month appointments), tenure track appointments. The University reserves the right to hire at any rank depending on the qualifications of the selected applicants. All faculty are expected to develop an extramurally-funded research program, be involved in scholarly activities, contribute to the PharmD curriculum, serve as a faculty advisor for PharmD students, and provide service to the College and University by serving on appropriate committees. Excellent communication skills and the ability to function in a team environment are essential qualities of these positions.

Three full-time faculty positions are available in the Dept. of Pharmaceutical Sciences (one in medicinal chemistry, one in pharmaceutics and one in pharmacology) at the assistant, associate or full professor rank. A PhD degree in the respective discipline is required or Pharm D or other doctoral degree with equivalent training. Preference will be given to candidates who have a pharmacy background and two or more years experience in academic pharmacy. Successful candidates will contribute to the appropriate pharmaceutical sciences lectures and laboratory components of the PharmD curriculum. All faculty members will be expected to contribute to the scholarly pursuits of the department in basic and applied research. It is expected that all new faculty will either have or will develop a research program that is complementary to those already existing within the department.

The review of applications will begin immediately and continue until the positions are filled. Rank and a highly competitive salary are commensurate with qualifications and experience. Interested candidates are invited to submit a letter of intent and provide their philosophy of teaching and research, a curriculum vitae and contact information for 3 professional references to the chair of the appropriate search committee.

For full details of the positions and application requirements, link to: **http://www.uhh.hawaii.edu/uhh/hr/jobs.php**.

Contact Information:
Anthony D. Wright, PhD
Associate Professor & Chair
Department of Pharmaceutical Sciences
College of Pharmacy
University of Hawaii at Hilo
60 Nowelo Street – Suite 101
Hilo, HI 96720
(808) 443-5900
adwright@hawaii.edu

Biomedical Science Faculty
Washington State University Spokane
Program in
Basic Medical Education – WWAMI

Applications are sought for up to four tenure-track faculty positions for the new WWAMI (Washington, Wyoming, Alaska, Montana, Idaho) Medical Education Program at Washington State University (WSU)-Spokane. These positions will be at the Assistant/Associate professor level, and will also be eligible to receive an affiliate faculty, non-tenure track appointment at the University of Washington School of Medicine.

Successful candidates will be expected to develop a strong, federally funded biomedical research program, as well as teach in one of the first year medical school courses. Preference will be given to those applicants with research interests in one of the existing areas of strength, including chromosome biology/DNA repair/epi-genetics, cancer biology, sleep and performance, substance abuse and addiction, reproductive biology, at risk families and children and translational and clinical research. Strong collaborative ties exist with the WSU Pullman campus. Further details about these positions including qualifications requirements may be found at the website **www.chr.wsu.edu**.

Further information about the WWAMI Program please see: **http://www.spokane.wsu.edu/academics/Health_Sciences/WWAMI**

Review of applications will begin **October 1, 2007**.

EEO/AA

USDA ars Agricultural Research Service
www.ars.usda.gov

RESEARCH GENETICIST
ANNOUNCEMENT NO: RA-07-067L
The position is located in the Subtropical Horticulture Research Station in Miami, Florida

DESCRIPTION OF DUTIES: The incumbent will conduct research on the mapping of genes in cacao (Theobroma cacao) regulating reproductive self-compatibility. This will require the development of appropriate pollination methods to evaluate this trait in a mapping population of 700 progeny. The objectives of the incumbent's research project will include: the identification and mapping of genomic regions in cacao associated with reproductive self-compatibility, mapping other traits of importance in the mapping population under study, and analytical support for plant selection and genetic diversity analyses. The incumbent is also the assistant investigator for a project to select new cacao cultivars and will provide analytic support for genetic diversity studies.

QUALIFICATION REQUIREMENTS: Ph.D. in Genetics or a closely related field is required. Professional knowledge in the fields of population and quantitative genetics and biostatistics are preferred.

Information on salary and application procedures for postdoctoral positions is available at: **http://www.afm.ars.usda.gov/divisions/hrd/hrdhomepage/vacancy/pd962.html**.

Information on employee benefits is available at: **http://www.usajobs.opm.gov/ei61.asp**.

For specific information on the duties and responsibilities of this position or to submit an application, contact: **Dr. Juan C. Motamayor, Subtropical Horticulture Research Station, USDA/ARS, 13601 Old Cutler Road, Miami, Fl 33158; Phone: 305-969-6426; Fax: 305-969-6410; Email: jc.motamayor@ars.usda.gov.**

THE U.S. DEPARTMENT OF AGRICULTURE IS AN EQUAL OPPORTUNITY EMPLOYER.

POSITIONS OPEN

TENURE-TRACK or TENURED FACULTY POSITIONS
Indiana University, Bloomington, Indiana
Biochemistry/All Ranks

The Department of Chemistry at Indiana University has a distinguished record of scientific achievement and is in the midst of significant additions to its faculty. Several new initiatives are underway in Bloomington, Indiana, including the completion of a new Center for interdisciplinary research. We invite applications for tenure-track faculty in biochemistry beginning August 2008. Successful candidates will possess outstanding credentials and be expected to develop a vigorous, independent research program. All faculty members contribute to teaching and curricular development. Candidates with interests in all aspects of biochemistry but especially areas such as chemical biology, structural biology, and proteomics will be considered in a new human biology program. Individuals of advanced stature with proven performance in research and teaching are encouraged to apply and will be considered at the **ASSOCIATE** or **FULL PROFESSOR** level.

Applicants must specify the area or areas in which they have special competence, and include curriculum vitae. A Ph.D. degree in chemistry is required and postdoctoral experience is strongly preferred. **ASSISTANT PROFESSOR** candidates should include a summary of future research plans and arrange to have four letters of recommendation forwarded to the Department. Review of applications will begin upon receipt and will continue until the positions are filled. Send applications to: **Professor Richard D. DiMarchi, Chairman, Biochemistry Search Committee, Department of Chemistry, 800 E. Kirkwood Avenue, Indiana University, Bloomington, IN 47405. Fax: 812-856-5050; e-mail: chemchair@indiana.edu.** *Indiana University is an Affirmative Action/Equal Opportunity Employer and especially encourages applications from women and members of minority groups.*

Ph.D. **TENURE-TRACK BIOCHEMIST** to start fall 2008. Commitment to undergraduate teaching and research in biochemistry, teaching organic and/or general chemistry required. Send letter, curriculum vitae, teaching philosophy, research plan, transcripts, and three letters of recommendation to: **Department of Chemistry and Biochemistry, Colorado College, 14 E. Cache La Poudre, Colorado Springs, CO 80903** by October 15, 2007. **Website: http://www.coloradocollege.edu/dept/CH/.**

The College is an Equal Opportunity Employer that does not discriminate on the basis of race, color, age, religion, sex, sexual orientation, national origin, or disability in its educational programs, activities, or employment practices. It is committed to increasing the diversity of our community. Candidates who contribute to that goal are particularly encouraged to apply, identifying experiences which will add to that diversity.

POSTDOCTORAL OPPORTUNITIES

POSTDOCTORAL FELLOWS
Harvard University

The six Environmental Fellows at Harvard University who will start work in September 2008, will be outstanding scholars with a Doctorate in any field and a research interest in the environment. Each Fellow will work with a host faculty member in the host's laboratory or office. Excellent salary and benefits. Apply by January 15, 2008. Details at **website: http://www.environment.harvard.edu.** *Harvard is an Equal Opportunity, Affirmative Action Employer.*

POSTDOCTORAL RESEARCH POSITION
Yale School of Medicine

Two Postdoctoral positions are available to study membrane proteins that catalyze intramembrane proteolysis. Experience in crystallography or membrane protein biochemistry is required. Please send curriculum vitae and names of three references to: **Dr. Ya Ha, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06520 U.S.A. E-mail: ya.ha@yale.edu.**

POSITIONS OPEN

UNIVERSITY of ROCHESTER

UNIVERSITY of ROCHESTER

The Department of Chemistry invites applications for one or more positions in organic and inorganic chemistry, broadly defined, at the **ASSISTANT, ASSOCIATE, and FULL PROFESSOR** levels. Candidates are expected to establish an outstanding program of original research and be effective teachers at the graduate and undergraduate levels. Applicants should send curriculum vitae, a statement of research plans, teaching interests, and arrange for three letters of recommendation to be sent, preferably in electronic form, to **Ms. Karen Dean, e-mail: dean@chem.rochester.edu,** or by mail to: **Chemistry Faculty Search Committee, c/o Ms. Karen Dean, Department of Chemistry, University of Rochester, RC Box 270216, Rochester, NY 14627-0216.** Review of applications will begin on October 15, 2007. *The University of Rochester is an Equal Opportunity Employer. Women and minority candidates are strongly encouraged to apply.*

MOLECULAR BIOLOGIST
Colgate University

The Department of Biology seeks a tenure-stream **ASSISTANT PROFESSOR** to start August 2008. Ph.D. or expectation of completion this academic year required; teaching and postdoctoral research experience desirable. The successful candidate will contribute to a foundation course called Molecules, Cells, and Genes, teach elective courses including microbiology, contribute to a capstone seminar in molecular biology, and participate in university-wide programs. The appointee will join a biology faculty deeply committed to a strong, research-oriented program involving undergraduate students and will add to this effort by offering a research tutorial in their area of interest; opportunities also exist to lead Colgate's unique semester-long program at the NIH. The Department offers excellent teaching and research facilities. Applications are especially encouraged from candidates whose research is focused in the area of microbiology, virology, or immunology. Please forward a letter of application with curriculum vitae, transcripts, and separate statements of teaching philosophy and research interests to: **Dr. Nancy Pruitt, Chair, Molecular Biology Search, Department of Biology, Colgate University, Hamilton, NY 13346-1398,** and also arrange to have three letters of recommendation sent to this address. Review of applications will begin October 7, 2007, and continue until the position is filled. We intend to begin interviewing candidates by the end of October 2007. Applicants with dual-career considerations can find postings of other employment opportunities at Colgate and at other institutions of higher education in upstate New York at **website: http://www.upstatenyherc.org.** *Colgate University is an Equal Opportunity/Affirmative Action Employer. Developing a diverse faculty and staff furthers the University's academic mission for our increasingly diverse student body.*

Applications are invited for a **RESEARCH ASSISTANT PROFESSOR** (nontenure track) position in the Department of Chemistry and Molecular Biology to manage the Core Biology Facility. Responsibilities include: consulting/collaborating with research groups, overseeing and participating in training of students, writing/submitting grant proposals. Research projects in the Center involve the synthesis of protease inhibitors and efficacy analysis in in vitro and cell-based assays, as well as cancer and asthma research. Requires a Ph.D. and experience in molecular biology, cell biology, pharmacology, or related field. Send curriculum vitae and three letters of reference to: **Rose Nichols, Center for Protease Research, North Dakota State University, P.O. Box 5516, Fargo, ND 58105,** or **e-mail: rose.nichols@ndsu.edu** by October 10, 2007, or until position is filled. See **website: http://www.ndsu.edu/jobs** for full details. *NDSU is an Equal Opportunity Employer.*

POSITIONS OPEN

FACULTY OPENING
Stanford University
Department of Mechanical Engineering

The Department of Mechanical Engineering at Stanford University invites applications for a tenure-track faculty position at the **ASSISTANT PROFESSOR** level. We give high priority to the overall originality and promise of the candidate's work rather than the candidate's sub-area of specialization within mechanical engineering.

We seek applicants from all areas of mechanical engineering whose research lies at the frontier of fields that support the Department's vision of biology as a discipline in mechanical engineering.

An earned Ph.D., evidence of the ability to pursue a program of research, and a strong commitment to graduate and undergraduate teaching are required. The successful candidate will be expected to teach courses at the graduate and undergraduate levels and to build and lead a team of graduate students in Ph.D. research.

Applications should include curriculum vitae, a list of publications, one-page statements of research vision and teaching interests and the names and addresses of five references. Candidates are requested to ask that references send letters directly to the Search Committee. Please submit these materials by December 17, 2007, to: **Professor Ron Hanson, Search Committee Chair, Building 520, Room E, Stanford University, Stanford, CA 94035-3032;** or via electronic mail to **e-mail: levita@stanford.edu.**

For additional information contact **Professor Hanson.** The review of applications will begin on January 2, 2008; however, applications will be accepted until the position is filled.

Stanford University is an Affirmative Action, Equal Opportunity Employer.

FACULTY POSITION in MOLECULAR BIOPHYSICS
Johns Hopkins University School of Medicine

The Department of Biophysics and Biophysical Chemistry **(website: http://biophysics.med.jhmi.edu)** seeks outstanding candidates for the position of **ASSISTANT PROFESSOR.** Applications are sought in all areas of molecular biophysics and biophysical chemistry, including, but not limited to, enzymology, structural biology, single molecule studies, computational biophysics, biological spectroscopy, and mechanistic biochemistry. Priority will be given to applications received by November 1, 2007. Please submit paper copies of curriculum vitae, a summary of current and proposed research, and arrange to have three letters of recommendation sent to:

Search Committee
Department of Biophysics and Biophysical Chemistry
Johns Hopkins University School of Medicine
WBSB 713
725 North Wolfe Street
Baltimore, MD 21205-2185
Fax: 410-502-6910

The Johns Hopkins University is an Equal Opportunity Employer.

NATIONAL UNIVERSITY of SINGAPORE
Department of Chemical and Biomolecular Engineering

The Department of Chemical and Biomolecular Engineering at National University of Singapore invites applications for **TENURE-TRACK FACULTY POSITIONS** at all levels. The Department is one of the largest internationally with excellent in-house infrastructure for experimental and computational research. A Ph.D. in chemical engineering or related areas and a strong research record with excellent publications are required. Please refer to **website: http://www.chbe.nus.edu.sg/** for more information on the areas of interest and for application details. Applicants should send full curriculum vitae (including key publications), a detailed research plan, a statement of teaching interest, and a list of names of at least three references to: **Professor Raj Rajagopalan, Head of Department (attention: Ms. Nancy Chia, e-mail: nancychia@nus.edu.sg).**

Science Foundation Ireland (SFI)

The President of Ireland Young Researcher Award (PIYRA)

The President of Ireland Young Researcher Award (PIYRA) is a prestigious award for outstanding early career researchers in science and engineering from around the world to carry out their research in third level institutions in Ireland.

Awardees will be selected on the basis of exceptional accomplishments in engineering and science disciplines that underpin Information and Communications Technology (ICT) and Biotechnology (BIO), and creative research plans that are built on work that has attracted international attention.

PIYRA grants are up to €1 million (direct costs) over 5 years

Applicants for the PIYRA competition must have been awarded a PhD or equivalent within the last 5 years. Potential candidates for the award must contact any participating Irish third level institution and request consideration by the institution to be one of their nominees.

The deadline for submissions is October 17th 2007
Full details on PIYRA may be obtained on the SFI website www.sfi.ie

Built for Research

NDP National Development Plan 2007 - 2013

sfi science foundation ireland fondúireacht eolaíochta éireann

Science Foundation Ireland
Wilton Park House, Wilton Place, Dublin 2, Ireland
tel +353 1 607 3200 *fax* +353 1 607 3201
email info@sfi.ie www.sfi.ie

POSITIONS OPEN

TWO TENURE-TRACK POSITIONS
University of Denver
Department of Chemistry and Biochemistry

As a part of the Integrated Molecular Life Sciences and Biophysics (IMLSB) Initiative in the Division of Natural Sciences and Mathematics, the Department of Chemistry and Biochemistry invites applications for two tenure-track positions to commence September 1, 2008, in the broadly defined areas of biochemistry and molecular biophysics and organic/bioorganic chemistry. The successful candidates must have a Ph.D. and postdoctoral experience in appropriate fields, will develop an extramurally funded research program, will supervise graduate and undergraduate research, and will teach undergraduate and graduate courses. We intend to fill one position with **OPEN RANK** and the second position at the **ASSISTANT PROFESSOR** level. For a detailed description of the IMSLB, please refer to **website: http://www.biochem.du.edu/IMLSB/.**

All candidates must apply online at **website: https://www.dujobs.org.** Please attach the following documents: curriculum vitae, description of teaching and research experience, and statements of teaching philosophy and research interests. By mail, please submit two recent publications. Also have three letters of recommendation sent to the following address: **University of Denver, Chemistry and Biochemistry Faculty Search, Attn: Laurel Shurtleff, 2190 E. Iliff Avenue, Olin Hall 202, Denver, CO 80208.** Review of applications will begin on October 15, 2007, and will continue until the positions are filled.

ASSISTANT PROFESSOR of BIOLOGY
Linfield College

The College seeks applicants for a tenure-track Assistant Professor with a specialization in plant evolutionary biology beginning July 1, 2008. Possible areas of specialty may include, but are not limited to, plant systematics, population genetics, and genome evolution. Four courses taught annually include: an evolution course with a laboratory or field component for biology majors; an additional course with laboratory or field component in area of specialty for biology majors; participation in an introductory course for biology majors; a nonmajors course in area of specialty. Successful applicants will demonstrate a commitment to, and potential for, developing a vigorous research program with undergraduates. Ph.D. in biology or related field is required; postdoctoral experience is preferred. Send application letter, curriculum vitae, statements of teaching philosophy and research interests specific to this position, undergraduate and graduate transcripts, and three letters of reference by October 15, 2007, to: **Dr. J. Christopher Gaiser, Linfield College, Unit A468, 900 S.E. Baker Street, McMinnville, OR 97128.** Electronically submitted applications will not be accepted. Additional information regarding this position may be found at **website: https://www.linfield.edu/humanresources/teaching.php.**

CHEMICAL BIOLOGY/BIOCHEMISTRY. Tenure-track joint appointment in biology and chemistry. Primary responsibility will be to teach courses in the Biochemistry and Molecular Biology Program including introductory courses in cell and molecular biology, biochemistry, and appropriate upper-level courses, as well as directing undergraduate research. Participation in the College's interdisciplinary programs, including First Year Seminar is expected, as is directing undergraduate research as part of Wooster's Independent Study Program. Ph.D. required in the area of chemical biology, biochemistry, molecular biology, or a related field. After completing a pre-application at **website: http://www.wooster.edu/biology/application.html,** send curriculum vitae, official undergraduate and graduate transcripts, statement of teaching philosophy, description of research plans, and three letters of reference to: **William Morgan, Chairperson, Biochemistry and Molecular Biology Program, 931 College Mall, Wooster, OH 44691.** Review of applications will begin October 1, 2007, and continue until the position is filled. *Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

PIONEER
A DuPont Company

RESEARCH DIRECTOR

An experienced Scientist is required to lead a group of researchers responsible for advancing our yield enhancement initiative and for delivering products that are transgenically-enhanced for increased yield and productivity. This position also will fill a requirement for leadership in developing the next generation of yield-enhanced crops requiring multiple transgenes.

The successful candidate will have a Ph.D. in biological sciences and 10 to 12 years of experience in area of specialty or unique scientific skills. The person in this leadership position will be knowledgeable of the latest techniques and approaches to achieving enhanced, stable yield in crop plants. Individual will evaluate, manage, and coordinate research activities within the yield enhancement group of the Agronomic Traits Department. Outstanding supervision, management, communication, and interpersonal skills will be essential to success. This person will be expected to work crossfunctionally both within the Department and across other departments of the Crop Genetics Research and Development organization. An understanding and knowledge of plant breeding is crucial. Knowledge of molecular techniques, approaches, and gene expression is critical.

To learn more about this position and to apply, please go to **website: http://www.pioneer.com/careers.** *Equal Opportunity Employer.*

BIOLOGY FACULTY POSITIONS

Two tenure-track, **ASSISTANT PROFESSOR** positions, one in environmental science and one in restoration ecology, will be available in the Department of Biology and Physics at Kennesaw State University beginning August 2008. Applicants should have a strong potential for developing an externally funded research program involving undergraduates. Preference will be given to applicants with demonstrated excellence in teaching at the college level. An earned Doctorate in an appropriate discipline is required. For a complete description of positions, go to **website: http://www.kennesaw.edu/facultypositions/.** Review of applications will commence on 12 October 2007, and will continue until the position is filled. Submit a letter describing qualifications for the position, a statement of teaching philosophy, a statement of research interests, current curriculum vitae, graduate transcripts, and the names, addresses, telephone numbers, and e-mail addresses of three references to: **Dr. Bill Ensign, Restoration Ecology Search Committee** or **Dr. Heather Sutton, Environmental Science Search Committee; #1202, Kennesaw State University, 1000 Chastain Road, Kennesaw, GA 30144-5591.** *Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.*

MICROBIOLOGIST. The Department of Biological Sciences, California State University, East Bay, is seeking a Microbiologist for appointment to a tenure-track position at the level of **ASSISTANT PROFESSOR,** beginning fall 2008. We desire applicants who are committed to excellence in teaching and the development of an innovative, externally funded research program at an institution that is intent on fostering a culturally diverse intellectual community. The primary teaching responsibility will include undergraduate and Master's level courses in microbiology. A Ph.D. and postdoctoral experience are required. Submit curriculum vitae, research and teaching plans, selected reprints, and three letters of recommendation as hard copy to: **Microbiologist Search Committee, Department of Biological Sciences, California State University, East Bay, Hayward, CA 94542.** Review of applications will begin on November 1, 2007, and will continue until the position is filled. Direct inquiries to the **Chair of the Search Committee: e-mail: carol.lauzon@csueastbay.edu.** *Equal Opportunity Employer.*

POSITIONS OPEN

TENURE-TRACK BIOCHEMIST, Hamilton College, invites applications for a tenure-track position in biochemistry beginning July 2008. An entry-level appointment is targeted, but appointment of a senior scholar is possible. Ph.D. and postdoctoral or equivalent experience required.

Applicants must be committed to undergraduate education with interest in teaching an increasingly diverse student population and demonstrate excellence, or the potential for excellence, in teaching and research with undergraduates. Primary teaching responsibilities will be in biological chemistry with additional responsibilities in introductory chemistry, research methods, and other courses in the candidate's areas of expertise. The successful candidate will be expected to guide student research during the summer and advise the required Senior Project during the academic year. Excellent startup support will be provided. You will join a group of committed teacher/scholars who insist on excellence in teaching and have a passion for educating students through one-on-one mentoring of research. We work in a supportive collegial environment with superb administrative support in a new state-of-the-art facility.

Further information about Hamilton and the Department can be found at **website: http://www.chem.hamilton.edu.** Please send curriculum vitae, undergraduate and graduate transcripts, statements describing teaching interests and research plans, and arrange for three letters of recommendation to be sent by October 12, 2007, to: **Karen S. Brewer, Chair, Department of Chemistry, Hamilton College, 198 College Hill Road, Clinton, NY 13323.** *Hamilton College is an Equal Opportunity, Affirmative Action Employer and is committed to diversity in all areas of the campus community. Hamilton provides domestic partner benefits.*

ACADEMIC PHYSICIAN/SCIENTIST. The Division of Nephrology and Hypertension at Harbor-UCLA Medical Center offers a mid-level **FACULTY POSITION** with an appointment at the David Geffen School of Medicine at UCLA to an M.D. or M.D./Ph.D. scientist. Position includes substantial protected time for research. Qualified applicants should be in the mid level of their careers with an independent research program in a basic science discipline. Harbor-UCLA Medical Center is a major affiliate of UCLA. Many basic and clinical groups of investigators providing broad opportunities for collaboration within and across fields of medical research are active within the Division, outside the Division on the Harbor campus, and at UCLA. **Sharon G. Adler, M.D., Chief,** and **Raimund Hirschberg, M.D., Associate Chief for Research,** invite your application. Please send a brief description of your research, career goals, curriculum vitae with bibliography, and references to: **Ms. Kathy Rowley, Division of Nephrology and Hypertension, LABioMed, 1124 West Carson Street, Torrance, CA 90502; e-mail: krowley@labiomed.org.** *Equal Opportunity Employer.*

MASSACHUSETTS INSTITUTE of TECHNOLOGY
Department of Chemistry

The Massachusetts Institute of Technology Department of Chemistry invites applications for tenure-track appointments beginning July 2008. Applicants with teaching and research interests in biological, organic, inorganic, and physical chemistry are encouraged to apply. The appointments will be the rank of **ASSISTANT PROFESSOR,** but outstanding senior applicants could be considered.

A completed application will include curriculum vitae, a one-page summary of research plans, two or more research proposals, and three letters of recommendation. Application instructions will be posted by September 3, 2007, on MIT Chemistry's **website: http://web.mit.edu/chemistry/www/index.html.** To receive full consideration completed applications must be received by October 1, 2007.

MIT is an Equal Opportunity/Affirmative Action Employer. Applications from women, minorities, veterans, older workers, and individuals with disabilities are strongly encouraged.

POSITIONS OPEN

Professor of Sustainable Animal Agriculture and Sesnon Endowed Chair in Animal Science

Department of Animal Science
University of California, Davis, CA

The Department of Animal Science in the College of Agricultural and Environmental Sciences seeks applicants for a faculty position: Professor of Sustainable Animal Agriculture and Sesnon Endowed Chair in Animal Science. We seek outstanding applicants for appointment at the Associate or Full Professor rank. Research accomplishments should provide evidence of a strong and identifiable interest in coordinated inter-disciplinary research, where the objective is to investigate and improve the contribution of animals to a sustainable system of food production that emphasizes environmental stewardship. As holder of the Sesnon Chair (a five year term with appointment renewable on successful review) the Department of Animal Science expects the successful candidate to be a recognized leader who will build a departmentally as well as campus-based collaborative program of excellence in sustainable animal agriculture. Species expertise should be in livestock, poultry or aquatic organisms of food production relevance; disciplinary expertise should be relevant to the fields of animal science/animal biology.

The successful candidate will exhibit a well-defined interest in establishing an innovative program in agricultural sustainability with a demonstrated record of curriculum development and teaching excellence. The appointee will contribute to the new interdepartmental major in Sustainable Agriculture. Mentoring of graduate students, undergraduate student instruction and advising, participation in outreach programs, curricular development, and performance of University service are expected. The successful candidate is expected to develop a research, teaching and outreach program consistent with the missions of the Agricultural Experiment Station. The position is a nine-month tenure track appointment; eleven-month term employment to be offered and continued based upon academic personnel review. Applicants should submit materials as directed by the following website: **http://animalscience.recruitments.ucdavis.edu/**. Deadline is **October 31, 2007**. Questions call **(530)-752-7018**.

UC Davis is an Affirmative Action/Equal Employment Opportunity Employer and is dedicated to recruiting a diverse faculty community. We welcome all qualified applicants to apply, including women, minorities, veterans, and individuals with disabilities.

MEETINGS

11th STS Joint Meeting

in association with study groups of the German Society for Cell Biology (DGZ), the German Society for Immunology (DGfI) and the Society for Biochemistry and Molecular Biology (GBM)

SIGNAL TRANSDUCTION:

Receptors, Mediators and Genes

Organizers:
Ralf Hass, Hannover
Karlheinz Friedrich, Jena
Ottmar Janssen, Kiel
Frank Entschladen, Witten
and the STS-advisory board

Hilton Hotel, Weimar, Germany
November 01 - 03, 2007

http://www.sigtrans.de

Abstract Deadline: September 15th

Confirmed Keynote Speakers:
Malcolm Alison, London, UK
Pidder Jansen-Dürr, Innsbruck, Austria
Christof von Kalle, Heidelberg, Germany
Avi Kupfer, Baltimore, MD, USA
Peter Parker, London, UK
Lawrence Samelson, Bethesda, MD, USA

Special Focus Symposium 2007:
Imaging Technologies -
from Intravital Microscopy to Molecular Analyses

Workshop Topics:
Immune Cells
Receptor-triggered Pathways
Adhesion, Motility, Morphology
DNA Modification and Cell Death
Oxidative Stress and Senescence
Tumor Development and Cancer Therapy
Signal Alterations induced by Pathogens
Cellular Differentiation/Dedifferentiation and Stems Cells
Miscellaneous

POSITIONS OPEN

CHAIR, DEPARTMENT of CELL and DEVELOPMENTAL BIOLOGY
University of Colorado School of Medicine

The University of Colorado School of Medicine invites nominations and applications for the position of Chair of the Department of Cell and Developmental Biology. This position offers an excellent opportunity for an outstanding research scientist interested in leadership and academics to develop an important basic science department within a major research University. The Department is committed to excellence in research, teaching, and scholarship. The Chair will enjoy significant commitments from the Dean of the School of Medicine, including newly constructed laboratory and departmental facilities at the Anschutz Medical Campus, located in the northeast Denver metropolitan area. Applicants must have an M.D./Ph.D., M.D., or Ph.D. degree and have a track record of important, funded research in scientific areas relevant to Cell and Developmental Biology. The Search Committee is seeking individuals with administrative and leadership experience and expertise, a demonstrated commitment to education, and outstanding accomplishments in biomedical research. Applicants are invited to visit the departmental **website: http://www.uchsc.edu/cdb.** The review of applications will begin immediately and continue until the position is filled. Applications should include curriculum vitae, a one-page description of the applicant's vision for the Department and the names of three or more references. Submit applications electronically to: **Dr. Ann Thor, Search Committee Chair,** c/o **e-mail: laurie.bogue@uchsc.edu**. Applications are also accepted electronically at **website: http: //www.jobsatcu.com.** *The University of Colorado is committed to diversity and equality in education and employment. Women and minorities are encouraged to apply.*

MICROBIOLOGIST (TENURE TRACK), BIOLOGY. We seek a broadly trained Microbiologist as an **ASSISTANT PROFESSOR,** to teach microbiology, parts of the introductory biology sequence, a nonmajors course in area of expertise and an upper-level course in biology. Participation in the College's interdisciplinary programs, including First-Year Seminar, is expected, as is directing undergraduate research as part of Wooster's required Independent Study Program. Ph.D. research and/or teaching experience preferred. Ability to teach an upper-level course in any of the following areas will be considered a strength but is not essential for full consideration; plant biology, immunology, genetics, or bioinformatics/computational biology. After completing a pre-application at **website: http://www.wooster.edu/biology/application.html,** send curriculum vitae, statements on research and teaching philosophy, undergraduate and official graduate transcripts, and three letters of recommendation to: **Dr. Dean Fraga, Chair, Department of Biology, 931 College Mall, Wooster, OH 44691** by October 1, 2007, to receive full consideration. *Equal Opportunity/Affirmative Action Employer.*

SCIENTISTS

The newly erected Center for Genetic and Translational Medicine of the Albert Einstein College of Medicine is recruiting Scientists with Ph.D. and/or M.D. degrees whose research deals with human genetics of cardiovascular disease, molecular mechanisms of cardiovascular disease, development of novel translational strategies, and cardiac stem cells/regenerative approaches.

The Albert Einstein College of Medicine is a research-intensive institution located in New York City. It is affiliated with Montefiore Medical Center, a 1,200-bed hospital with extensive cardiovascular services including heart transplantation.

A generous recruitment package is provided. Please send curriculum vitae and statement of past, present, and future research interests to: **Dr. Richard N. Kitsis, Director, Cardiovascular Research Center, Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, 1300 Morris Park Avenue, Bronx, NY 10461. Telephone: 718-430-2609. E-mail: kitsis@aecom.yu.edu.** *Equal Opportunity Employer.*

POSITIONS OPEN

PLANT BIOLOGIST

Slippery Rock University of Pennsylvania invites applications for a tenure-track position in the Department of Biology beginning August 2008.

Teaching responsibilities: Introductory biology courses designed for the Liberal Studies Program, course in general botany, and contribution to other courses taken by biology majors. Other duties/expectations: Commitment to excellence in teaching in a liberal arts setting, establishment of a productive research program in the candidate's area of expertise that can involve undergraduates, recognition of Department goals and stated standards of performance, timely execution of work assignments, and contribution to Department, College, and University committees. The Department expects faculty to conduct creative, original research leading to publication in peer-reviewed, professional journals in the applicant's area of expertise. Qualifications: Earned Ph.D. in biological science (all-but-dissertation considered, Ph.D. much be completed by June 2008) and evidence of professional competence and ability to work productively with students and colleagues, successful performance in an on-campus interview including teaching and research presentations and a commitment to the education of diverse populations are required. Undergraduate teaching experience preferred.

Send letter of interest, curriculum vitae, statement of academic philosophy and research goals, teaching evaluations, graduate and undergraduate transcripts (official transcripts will be needed before hiring), and three letters from professional references to:

Chair
Plant Biologist Search Committee
Department of Biology
Slippery Rock University of Pennsylvania
Slippery Rock, PA 16057
Telphone: 724-738-2023
Fax: 724-738-4782

Review of applications will begin by October 5, 2007, and continue until position is filled. Visit our web page at **website: http://www.sru.edu.** *Background investigation required for employment. Slippery Rock University of Pennsylvania is a member of the State System of Higher Education and is an Affirmative Action/Equal Opportunity Employer.* ***TTY 724-738-4881.***

ASSISTANT/ASSOCIATE PROFESSOR
Department of Biochemistry and Molecular Biology
State University of New York
Upstate Medical University

We seek applications to fill one or two tenure-track positions at either the **ASSISTANT or ASSOCIATE PROFESSOR** levels from individuals studying fundamental molecular processes in eukaryotic organisms. We encourage applications in structural biology, genomics, membrane biology, and bioinformatics. The successful applicants will be expected to develop well-funded research programs and to contribute to medical and graduate teaching. We offer a highly competitive startup package and salary. Further information about the Department can be found at **website: http://www.upstate.edu/biochem.**

Candidates should have a Ph.D. or equivalent, postdoctoral experience, and a strong publication record. Applicants should e-mail a PDF file containing curriculum vitae, a summary of research accomplishments, and future research plans to **e-mail: biochem@upstate.edu.** In addition, three letters of reference should be mailed directly to: **Dr. Barry E. Knox, Search Committee Chair, Department of Biochemistry and Molecular Biology, 750 East Adams Street, Syracuse, NY 13210.**

Review of applications will begin on November 1, 2007, and continue until the positions are filled. *Women and minorities are highly encouraged to apply. Upstate Medical University is an Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

AWARDS

POSITIONS OPEN

ASSISTANT PROFESSOR of BIOLOGY ANIMAL PHYSIOLOGIST

Augustana College invites applications for a tenure-track Assistant Professor position in the Department of Biology beginning September 2008. Duties include teaching two courses each semester. These will include introductory biology, human physiology, and an advanced undergraduate course in general physiology. While teaching is a major component of the position, productive research involving undergraduates is expected and is a longstanding tradition in the Department. The College is situated in an area experiencing rapid growth in biomedical and biotechnology research, offering collaboration opportunities in various research areas. Applicants must possess a Ph.D. A commitment to the mission of a church-related liberal arts college is expected.

Salary is competitive and dependent upon qualifications; excellent fringe benefits are included.

Review of applications will begin immediately and close on October 5, 2007. Visit us at **website: http://www.augie.edu** or contact the **Department Chair, e-mail: steven.matzner@augie.edu, telephone: 605-274-4821** for information.

Please send a letter of application, including teaching philosophy and goals for professional development, copies of undergraduate and graduate transcripts, curriculum vitae, and three letters of reference to the: **Dean of the College, Augustana College, 2001 S. Summit Avenue, Sioux Falls, SD 57197, telephone: 605-274-4110, fax: 605-274-5547.** *Augustana College is an Equal Opportunity/Affirmative Action/Title IX Employer. Qualified minority applicants are encouraged to apply. Applicants must comply with the Immigration Reform and Control Act, and are required to submit official transcripts upon employment.*

CHIEF
Illinois Natural History Survey

Nominations and applications are invited for the position of Chief of the Illinois Natural History Survey, a Division of the Illinois Department of Natural Resources and an affiliated agency of the University of Illinois at Urbana, Champaign. The Survey is Illinois' premier agency for basic and applied research and service on the biological resources of the state. The staff consists of nearly 200 scientists and support personnel. The total annual budget of $16 million is comprised of a state appropriation plus a complex array of grants and contracts. The Chief is the Survey's top administrator with responsibility for the staff, programs, and finances of the Survey, and is the principal interface with state and federal agencies, interest groups, and the public. The candidate must possess a Ph.D. in the biological sciences. The candidate must have a research/publication record; demonstrated strong management, interpersonal and leadership skills; and demonstrable written and verbal communication skills. Experience in successfully managing a complex scientific organization and interacting with governing boards and advisory groups is highly desirable. For application requirements and complete position description visit our **website: http://www.inhs.uiuc.edu/opportunities.** E-mail any questions to **e-mail: hroffice@inhs.uiuc.edu.**

DIRECTOR, KONZA PRAIRIE BIOLOGICAL STATION
Kansas State University

The Division of Biology at Kansas State University (KSU) invites applications for the position of Director of the Konza Prairie Biological Station (KBSU). KPBS is a 3,487-hectare tallgrass prairie preserve owned by the Nature Conservancy and KSU and is operated as a research station by the KSU Division of Biology **(website: http://www.ksu.edu/konza).** More information about the position and materials to be submitted with your application can be found at **website: http://www.ksu.edu/biology/bio/news.htm.** Review of applications will begin September 24, 2007, and continue until the position is filled. *KSU is an Equal Opportunity/Affirmative Action Employer, and actively seeks diversity among its employees.*

POSITIONS OPEN

The Pomona College Neuroscience Program and Biology Department seek applications for a tenure-track **ASSISTANT PROFESSOR of BIOLOGY and NEUROSCIENCE** who studies the neural mechanisms underlying behaviors using a molecular, cellular, or systems level approach. The successful candidate will contribute to an introductory neuroscience course, offer at least one upper-division course with laboratory in his/her area of expertise, and supervise senior theses. We are seeking outstanding candidates with the ability to integrate undergraduates into an active experimental research program and a demonstrated commitment to recruiting and retaining students from underrepresented groups in the sciences. Competitive startup funds will be provided. Postdoctoral experience is preferred. Candidates should submit curriculum vitae, a statement of teaching philosophy including descriptions of proposed upper-level courses, a statement of research interests, reprints/preprints, graduate school transcripts, and three letters of recommendation to: **Dr. Nicole Y. Weekes, Chair, Neuroscience Search Committee, Department of Biology, 175 W. 6th Street, Pomona College, Claremont CA 91711-6339.** Review of applications will begin on October 19, 2007, and continue until the position is filled.

Pomona College is a highly selective, coeducational liberal arts college located 35 miles east of Los Angeles. Pomona College is an Equal Opportunity Employer and especially invites applications from women and members of underrepresented groups.

The Center for Genomics and Bioinformatics **(website: http://cgb.indiana.edu)** at Indiana University (Bloomington) seeks M.S.-level candidates for the position of **BIOINFORMATICS STAFF SCIENTIST** to join our team. Skills include programming, sequence analysis, statistical analysis with R, web programming, mySQL, microarray analysis, excellence in both written and spoken English. Responsibilities include participation in independent research; consulting support; teaching bioinformatics workshops; and installing/maintaining bioinformatics software. Appointments will be at the rank of **RESEARCH ASSOCIATE** and salary will be commensurate with experience. Direct all inquiries to **e-mail: jobs@cgb.indiana.edu.** Positions are open now and applications will be accepted until positions are filled, those received by September 30, 2007, will be assured full consideration. Submit a cover letter, curriculum vitae, and a brief description of your background/interests. Arrange for three reference letters to be sent directly to us. Send materials to: **Position #CGB-011, Center for Genomics and Bioinformatics, Indiana University, 1001 E. 3rd Street, Bloomington IN 47405-3700.** *Indiana University is an Affirmative Action Equal Opportunity Employer.*

The Division of Experimental Pathology, Department of Pathology and Laboratory Medicine, University of Tennessee Health Science Center, is recruiting **RESEARCH FACULTY** to complement expertise in cancer research in a highly collaborative scientific environment using molecular, genetic, or cellular approaches. Laboratory space in a newly built cancer research building, salary support, and startup funds are available. Candidates should have a demonstrated record of research accomplishments and should have current research funding or the potential to establish an independent, funded research program. Academic rank will be commensurate with experience. Contact: Interested candidates should send their curriculum vitae, statement of research interests, and the names of three references to: **Lawrence M. Pfeffer, Ph.D., Muirhead Professor and Vice-Chair, Department of Pathology and Laboratory Medicine, 930 Madison Avenue, Room 530, UTHSC, Memphis, TN 38163; e-mail: lpfeffer@utmem.edu.** *The University of Tennessee is an Equal Employment Opportunity/Affirmative Action/Title VI/Title IX/Section 504/ADA/ADEA Institution in the provision of its education and employment programs and services.*

POSITIONS OPEN

ASSISTANT PROFESSOR, DEVELOPMENTAL BIOLOGIST
Department of Biology
California State University, Northridge

The Department of Biology at California State University, Northridge, invites applications to fill an Assistant Professor tenure-track position in developmental biology, with an anticipated starting date of August 2008. This tenure-track position involves teaching courses in developmental and cell biology with assignments in lower-division courses including introductory biology. The successful candidate is expected to develop a vigorous research program involving undergraduate and graduate (M.S.) students, seek extramural research funding, demonstrate teaching excellence, and provide effective instruction to students of diverse backgrounds in multicultural setting. Candidates must have a Ph.D. or equivalent doctoral degree and postdoctoral experience is expected. Candidates with expertise in any area of eukaryotic developmental biology will be considered. Applicants should send a cover letter, curriculum vitae, statement of teaching philosophy and research interests, reprints of up to three publications, and should arrange for three letters of recommendation to be sent to: **Chair, Department of Biology, California State University, Northridge, 18111 Nordhoff Street, Northridge, CA 91330-8303.** Applications in PDF-format are preferable **(e-mail: larry.allen@csun.edu).** Review of completed applications will begin on October 29, 2007, and will remain open until filled.

CSUN is an Equal Opportunity Employer committed to excellence through diversity.

ASSISTANT PROFESSOR
Utah State University

The Department of Chemistry and Biochemistry at Utah State University invites applications for a tenure-track position at the Assistant Professor level beginning fall 2008. Candidates must have a Ph.D. in chemistry or biochemistry and postdoctoral experience is desirable. The position requires the development of an externally funded research program in any area of biochemistry or bioinorganic chemistry emphasizing a physical chemical approach, and effective teaching in biophysical and physical chemistry laboratory courses. Applicants should submit curriculum vitae, concise descriptions of future research projects, a statement of teaching philosophy, and the names of three references online at **website: http://jobs.usu.edu** (requistion identification 050953). Evaluation of applications will begin October 15, 2007, and will continue until the position is filled. For further information please visit our **website: http://www.chem.usu.edu.** *Utah State University is an Equal Opportunity/Affirmative Action Employer committed to assembling a diverse faculty. Women and members of minority groups are strongly encouraged to apply.*

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